



# Paramètres biologiques et échocardiographiques et remodelage ventriculaire gauche après syndrome coronarien aigu avec sus-décalage du segment ST

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## THÈSE

Pour obtenir le diplôme de doctorat

Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE

Préparée au sein de l'Université de Caen Normandie

### Paramètres biologiques et échocardiographiques et remodelage ventriculaire gauche après syndrome coronarien aigu avec sus-décalage du segment ST

Présentée et soutenue par  
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Thèse soutenue publiquement le 16/12/2020  
devant le jury composé de

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## *Résumé*

Le remodelage ventriculaire gauche est une complication fréquente des patients ayant présenté un syndrome coronarien aigu, pouvant conduire à terme à une situation d'insuffisance cardiaque. Il est donc important de connaître les facteurs associés à la survenue d'un remodelage ventriculaire afin de dépister plus précocement les patients à plus haut risque d'insuffisance cardiaque et ainsi optimiser leur prise en charge. Ce travail comprend deux axes. Le premier porte sur la recherche de nouveaux paramètres d'imagerie associés à la survenue du remodelage. Nous avons dans un premier temps réalisé une revue de la littérature concernant la définition du remodelage ventriculaire gauche en imagerie par résonance magnétique. Puis, nous avons conduit deux études ayant pour but de rechercher une association entre (i) le strain atrial gauche et, (ii) le gradient de pression intraventriculaire gauche diastolique, évalués en échocardiographie 24-48 heures après le syndrome coronarien aigu et le remodelage ventriculaire gauche au cours du suivi. Le second axe porte sur les biomarqueurs associés au remodelage ventriculaire post-infarctus. Nous avons réalisé une revue de la littérature au sujet des biomarqueurs qui, dosés lors de l'hospitalisation initiale, sont associés à l'existence d'un remodelage lors du suivi. Nous avons ensuite étudié la valeur prédictive de deux biomarqueurs (la néprilysine et le coenzyme Q10) pour la survenue d'un remodelage ventriculaire gauche.

## *Abstract*

Left ventricular remodeling is a common complication in patients following acute myocardial infarction and may lead to heart failure. Some baseline parameters are associated with remodeling at follow-up, allowing to better discriminate patients with an increased risk of heart failure to optimize therapeutics. This work has two axes, focused on imaging and biological parameters associated with left ventricular remodeling, respectively. First, we reviewed past studies that defined remodeling using cardiac magnetic resonance imaging. Then, we studied the association between some echocardiographic parameters (left atrial strain and diastolic intraventricular pressure gradient) and left ventricular remodeling after ST-elevation myocardial infarction. In the other axis, we reviewed biomarkers that have been associated with left ventricular remodeling in prior studies. Then, we investigated the association between neprilysin and coenzyme Q10 levels and left ventricular remodeling in STEMI patients.

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## Liste des abréviations

|                               |                                                                                               |
|-------------------------------|-----------------------------------------------------------------------------------------------|
| <b>AMPC</b>                   | adénosine monophosphate cyclique                                                              |
| <b>ARA2</b>                   | antagoniste du récepteur AT <sub>1</sub> de l'angiotensine-II                                 |
| <b>ARNI</b>                   | inhibiteur de la néprilysine (angiotensin receptor-neprilysin inhibitor)                      |
| <b>CoQ10</b>                  | coenzyme Q10                                                                                  |
| <b>ERO</b>                    | espèces réactives en oxygène                                                                  |
| <b>FEVG</b>                   | fraction d'éjection ventriculaire gauche                                                      |
| <b>GPIVD</b>                  | gradient de pression intraventriculaire diastolique                                           |
| <b>IC</b>                     | insuffisance cardiaque                                                                        |
| <b>IEC</b>                    | inhibiteur de l'enzyme de conversion de l'angiotensine                                        |
| <b>IRM</b>                    | imagerie par résonance magnétique                                                             |
| <b>MMP</b>                    | matrix metalloproteinase                                                                      |
| <b>OG</b>                     | oreillette gauche                                                                             |
| <b>PRVG</b>                   | pressions de remplissage ventriculaire gauche                                                 |
| <b>RVG</b>                    | remodelage ventriculaire gauche                                                               |
| <b>SCA</b>                    | syndrome coronarien aigu                                                                      |
| <b>SNA</b>                    | système nerveux autonome                                                                      |
| <b>SRAA</b>                   | système rénine angiotensine aldostérone                                                       |
| <b>STEMI</b>                  | syndrome coronarien aigu avec sus-décalage du segment ST (ST-elevation myocardial infarction) |
| <b>TGF-<math>\beta</math></b> | transforming growth factor- $\beta$                                                           |

**TEP** Tomographie par Émission de Positons

**TM** temps mouvement

**VG** ventricule gauche

**VTD** volume télédiastolique

**VTs** volume télésystolique

# Introduction

Le syndrome coronarien aigu (SCA) est défini par la survenue d'une nécrose myocardique dans un contexte d'ischémie myocardique [1]. Il est courant de distinguer le syndrome coronarien aigu avec sus-décalage du segment ST (ST-elevation myocardial infarction) (STEMI) et le SCA sans sus-décalage du segment ST. En effet, les mécanismes physiopathologiques et la prise en charge des patients diffèrent significativement entre ces deux entités. La majorité des STEMI sont classés comme infarctus myocardique de type 1, c'est-à-dire en rapport avec un thrombus intracoronaire responsable d'une occlusion coronaire [2]. Il existe de rares situations de STEMI sans occlusion coronaire aiguë. Dans ce travail, nous utiliserons le terme STEMI pour désigner un SCA avec sus-décalage du segment ST en rapport avec une occlusion coronaire aiguë.

La stratégie de revascularisation dans le STEMI repose sur la reperfusion coronaire en urgence, par l'utilisation de moyens mécaniques (angioplastie primaire) et pharmacologiques (traitement fibrinolytique, antiagrégant plaquettaire ou anticoagulant). L'amélioration progressive de la prise en charge des patients ayant présenté un STEMI – et notamment la réduction des délais de prise en charge – a conduit à une diminution significative de la morbi-mortalité. La mortalité intrahospitalière est désormais estimée entre 4 et 12% en Europe [3] et la mortalité à 1 an, à 10% [4, 5]. L'amélioration du pronostic de ces patients à la phase aiguë a pour conséquence l'observation fréquente de complications à moyen ou long terme comme la survenue de troubles du rythme ventriculaire ou l'évolution vers l'insuffisance cardiaque (IC)). Une partie des patients vont ainsi présenter un remodelage ventriculaire gauche (RVG) au décours de leur STEMI, sous l'effet de mécanismes complexes associant

notamment perturbations hémodynamiques, inflammation et activation neurohormonale. Ces mécanismes d'action et les éventuelles cibles thérapeutiques qui en découlent sont un axe de recherche majeur pour améliorer encore le pronostic des patients en post-infarctus.

## **Le remodelage ventriculaire gauche après SCA**

La survenue d'un RVG au décours d'un STEMI est un facteur pronostique majeur, indépendamment de la fraction d'éjection ventriculaire gauche (FEVG) [6–8]. Il est donc important de disposer d'une définition consensuelle du RVG afin de pouvoir classer les patients selon l'existence ou non d'un RVG après l'infarctus. Il est également nécessaire de comprendre les mécanismes impliqués dans la survenue de ce RVG afin de pouvoir disposer de marqueurs prédictifs précoces dans le but d'adapter la prise en charge de ces patients.

### **Physiopathologie et mécanismes du RVG**

Le RVG est un processus visant initialement à compenser le dysfonctionnement du système cardiovasculaire en permettant de maintenir un débit cardiaque adapté aux besoins de l'organisme. Initialement bénéfique, le RVG va progressivement aboutir à une augmentation des volumes ventriculaires gauches, une augmentation des besoins myocardiques en oxygène (potentiellement pourvoyeur de nouvelles zones d'ischémie myocardique) [9], et éventuellement une fuite mitrale [10] et une altération de la FEVG.

Le SCA va entraîner une réponse inflammatoire et une activation neuro-hormonale. Ces systèmes vont conduire d'une part au remplacement des tissus nécrosés par une cicatrice fibrotique et d'autre part, à une hypertrophie des cardiomyocytes et à la survenue d'une fibrose interstitielle dans les tissus non directement concernés par l'infarctus [11]. Ce processus

dynamique concerne donc l'ensemble du myocarde, aussi bien en zone infarctée que dans les zones "remote" non directement touchées par l'infarctus.

L'ensemble du processus de RVG est habituellement divisé en 3 phases. La première est la phase inflammatoire et débute immédiatement après l'occlusion coronaire [12]. Un élément fondamental dans la régulation des phénomènes inflammatoires initiaux est l'expression de gènes codant pour des cytokines pro-inflammatoires, sous le contrôle du facteur nucléaire NF- $\kappa$ B [13]. Cette réponse inflammatoire intense active les cellules sentinelles résidentes, augmente la perméabilité des capillaires et conduit au recrutement de leucocytes [14, 15] dans le but de nettoyer les cellules nécrosées et les débris de la matrice extracellulaire, par l'intermédiaire de l'activité protéolytique de métalloprotéases matricielles (MMP pour matrix metalloproteinase) [16, 17]. La durée et l'amplitude de l'inflammation et de sa résolution sont des points fondamentaux de la qualité de la cicatrisation. Ainsi, une prolongation de la phase inflammatoire peut entraîner des lésions tissulaires propres, pouvant aboutir à une diminution de la fonction contractile, l'expansion de l'infarctus et contribuer au RVG [18, 19]. La seconde phase est la phase de réparation et de prolifération, sous le contrôle de TGF- $\beta$  (transforming growth factor- $\beta$ ), caractérisée par la résolution de l'inflammation, une augmentation du nombre de fibroblastes cardiaques et leur transformation en myofibroblastes, cellules capables de synthétiser des protéines matricielles. On assiste également à des phénomènes de néovascularisation [20–23]. La dernière phase est la phase de maturation où survient l'apoptose des cellules réparatrices encore présentes et l'organisation des fibres de collagène en systèmes réticulés.

De très nombreux travaux ont étudié les voies de signalisation mises en jeu dans le processus de cicatrisation tissulaire en post-infarctus [24, 25]. La plupart de ces voies de signalisation peuvent être régulées par l'activation neuro-hormonale mise en évidence

après un SCA. Le système rénine angiotensine aldostérone (SRAA) aboutit à la synthèse d'angiotensine-II dont les effets sont vasoconstricteurs, pro-inflammatoires, apoptotiques et fibrosants [26, 27]. Elle est aussi responsable d'une hypertrophie des cardiomyocytes et d'une réactivation de gènes fœtaux [27]. Il a été montré que le taux d'aldostérone est un facteur pronostic chez les patients ayant présenté un STEMI [28]. Le blocage du SRAA permet d'ailleurs de limiter le RVG post-infarctus et améliore le pronostic [29, 30]. Après un SCA, il existe également une augmentation de l'activité du système nerveux autonome (SNA), à l'échelle de l'organisme mais également au niveau du tissu cardiaque [31]. En réponse à une diminution du débit cardiaque, le SNA va induire une stimulation de la production d'adénosine monophosphate cyclique (AMPC) [32], activant ainsi la protéine kinase A. Il en résulte une augmentation de la concentration intracellulaire en calcium et la phosphorylation – et donc la régulation – de canaux ioniques [33, 34] et de plusieurs protéines intervenant dans le couplage excitation-contraction [35–39]. Ainsi, le SNA a des actions chronotrope  $\oplus$ , inotrope  $\oplus$  et lusitrope  $\oplus$ . L'activation prolongée du SNA va induire une modification de la densité et de la signalisation des récepteurs  $\beta$  [40, 41], et avoir une action pro-inflammatoire [42, 43], fibrosante [44, 45], apoptotique [46] et favorisant le stress oxydatif [45]. Une partie des lésions tissulaires au décours immédiat du SCA sont en rapport avec l'existence de lésions d'ischémie-reperfusion, dont les causes sont multiples : production d'espèces réactives en oxygène (ERO), altération de la régulation du calcium intracellulaire, dysfonction endothéliale [47], peroxydation des lipides, perturbations de l'énergétique cellulaire ou encore déficit en vitamines anti-oxydantes et en coenzyme Q10 [48–50]. Les mécanismes responsables du RVG post-SCA sont donc complexes et font donc notamment intervenir les systèmes neuro-hormonaux et les fonctions endothéliales et mitochondriales.

### **L'imagerie du RVG : définition et facteurs prédictifs de survenue**

Les bases mécanistiques du remodelage cardiaque et la caractérisation des liens entre le RVG et la progression de l'IC ont été les thèmes de l'*International Forum on Cardiac Remodeling* qui s'est tenu en 1998 [51]. Le RVG y a été défini comme les modifications de l'expression génomique ayant pour conséquences des changements à l'étage moléculaire, cellulaire ou interstitiel et aboutissant à des modifications de la taille, de la forme ou de la fonction du cœur et des vaisseaux. En pratique clinique quotidienne, il est proposé que la quantification du RVG se fasse sur des mesures des volumes télédiastolique et télésystolique du ventricule gauche (et donc aussi de la FEVG) mais aussi sur la masse du ventricule gauche (VG). Les premiers travaux cliniques sur le RVG datent de plus de 20 ans et utilisaient majoritairement l'échocardiographie [52, 53]. Le RVG a souvent été défini dans les études comme une augmentation d'au moins 20% du volume télédiastolique en échocardiographie entre un examen réalisé à la phase initiale du SCA et un second au cours du suivi [52]. L'imagerie par résonance magnétique (IRM) cardiaque possède une meilleure reproductibilité des mesures de volumes et de fonction du VG, et permet de visualiser la fibrose [54]. Pourtant, il n'existe aucune recommandation sur la façon de quantifier le RVG et notamment concernant la modalité d'imagerie, le délai de réalisation des examens d'imagerie ou encore la valeur seuil d'augmentation des volumes ventriculaires gauches à utiliser. Malgré cela, de très nombreuses publications ont proposé des paramètres prédictifs de survenue du RVG après SCA, que ce soit en échocardiographie [55–57] ou en IRM [58–60]. Certains de ces paramètres sont désormais communément admis, comme l'obstruction micro-vasculaire en IRM [61, 62], la taille de la zone infarctée [58–60] ou encore le strain longitudinal global en échocardiographie [55, 56].

## **Questions posées et objectifs du travail de thèse**

Ce travail a pour objectif d'apporter de nouvelles données sur les mécanismes d'action conduisant à la survenue d'un RVG au décours d'un STEMI et de rechercher de nouveaux paramètres prédictifs de sa survenue. Le but est de pouvoir dépister le plus tôt possible les patients qui ont le plus de risques d'évoluer vers un RVG au cours du suivi afin de pouvoir sélectionner ceux qui pourraient bénéficier d'une intensification du traitement.

Ce travail a été organisé en deux axes :

- Premier axe (imagerie) : étudier les définitions du RVG utilisées dans la littérature, en proposer une définition plus précise et rechercher de nouveaux outils d'imagerie permettant d'identifier précocement les patients qui évolueront ultérieurement vers un RVG après STEMI.
- Second axe (biologie) : rechercher de nouveaux marqueurs biologiques d'intérêt chez le patient ayant un STEMI afin de mieux prédire la survenue d'un RVG.

S'agissant d'un travail de recherche clinique portant sur la thématique du RVG au décours d'un STEMI, ce travail de thèse a débuté par la constitution d'une cohorte de patients, pris en charge pour un STEMI, la cohorte RESIST (pour REgistre des Soins et Interventions pour les syndromes coronariens aigus avec sus-décalage du segment ST, cf. page suivante). Les cohortes de patients étudiées dans les sous-parties de ce travail de thèse sont toutes issues de ce registre.

# Le registre RESIST

Le REgistre des Soins et Interventions pour les syndromes coronariens aigus avec sus-décalage du segment ST (RESIST) a débuté en juin 2015 et visait à recueillir des données démographiques, cliniques, biologiques et d'imagerie chez les patients admis pour un STEMI dans l'ancienne région Basse-Normandie. Les structures participantes à ce registre étaient les deux centres de cardiologie interventionnelle de la région (C.H.U. de Caen et Centre Hospitalier Privé St Martin, à Caen) ainsi que l'ensemble des centres hospitaliers généraux et des SAMU-SMUR de la région. Un des objectifs était de mieux connaître le parcours des patients pris en charge pour un STEMI dans notre bassin de population, notamment les délais de prise en charge.

## Données recueillies

Les données suivantes étaient saisies dans une base de données informatisée après recueil au format papier de la feuille de transmission des équipes SAMU-SMUR (spécialement éditée pour le registre), des données de la procédure de coronarographie en urgence, consultation de la base de données de l'établissement, et appel du patient à 3 mois de l'évènement initial  $\pm$  données échocardiographiques de suivi si le patient était d'accord pour avoir un suivi sur le centre (feuille d'information et recueil du consentement):

- données démographiques : âge, sexe, coordonnées
- antécédents, facteurs de risque cardio-vasculaires
- prise en charge à la phase aiguë, en pré-hospitalier : premier contact médical, lieu de prise en charge, appelant, parcours de prise en charge, stratégie de reperfusion, évènements cardio-vasculaires et traitements reçus

- coronarographie : lésion coupable, formule coronaire, lésions associées, gestes d'angioplastie réalisés
- $\pm$  biologie de routine et biobanque
- $\pm$  données échocardiographiques 2D/3D, initiale et au cours du suivi (6 mois) :

*valve aortique*

- gradient moyen trans-valvulaire, quantification d'une éventuelle fuite valvulaire aortique ou d'une sténose
- acquisition temps-mouvement avec doppler couleur
- mesure de l'intégrale temps-vitesse dans la chambre de chasse ventriculaire gauche en doppler pulsé, calcul du débit cardiaque

*valve mitrale*

- recherche et quantification d'une fuite mitrale (calcul de la surface de l'orifice régurgitant), étude du mécanisme de la fuite le cas échéant
- acquisition temps mouvement (TM) avec doppler couleur
- flux doppler pulsé transmitral

*ventricule gauche*

- diamètres télédiastolique et télésystolique
- volumes télédiastolique et télésystolique et calcul de la FEVG, en 2D (Simpson) et en 3D
- étude de la cinétique segmentaire du ventricule gauche
- épaisseur septale et de la paroi postérieure
- acquisition en doppler tissulaire : paroi latérale, paroi septale
- strain longitudinal global

*oreillette gauche*

- volume de l'oreillette gauche en 2D
- mesure du strain de l'oreillette gauche

#### *valve tricuspide et ventricule droit*

- fraction de raccourcissement du ventricule droit
  - doppler tissulaire à l'anneau tricuspide (onde S)
  - vitesse maximale du flux d'insuffisance tricuspide
  - mesure de l'excursion systolique du plan de l'anneau tricuspide en TM
- évènements intrahospitaliers et suivi à 3 mois (évènements cardiovasculaires majeurs)

### **Dates clefs**

- juin 2015 : obtention de l'accord de mise en place du registre (CPP Nord-Ouest III)
- juin 2015 : premières inclusions dans le registre
- octobre 2015 : début de la biobanque (tubes citratés)
- novembre 2015 : début des acquisitions échocardiographiques complètes 2D/3D
- janvier 2017 : utilisation de tubes secs et de tubes EDTA
- mai 2019 : gel de la base

### **Données disponibles dans le registre RESIST**

Entre le 1<sup>e</sup> juin 2015 et le 31 mai 2019, un total de 1865 patients ont été inclus dans le registre RESIST. Dans notre cohorte, 176 patients sont décédés durant l'hospitalisation initiale ou dans les 3 mois suivant la sortie d'hospitalisation. Le détail des données biologiques et échocardiographiques disponibles chez les 1689 patients restants sont résumées dans la

Table 1 : Données biologiques et échocardiographiques disponibles chez les 1689 patients du registre RESIST vivants à 3 mois de la sortie d'hospitalisation. Des données échocardiographiques complètes (à la phase aiguë et dans le suivi sont disponibles pour 168 patients (en bleu). Parmi ces patients, nous disposons de tubes secs et EDTA pour 63 d'entre eux (en vert), nous permettant de réaliser des dosages de biomarqueurs d'intérêt.

| Prélèvements sanguins disponibles | ETT initiale |                  |            | ETT de suivi disponible | Total |
|-----------------------------------|--------------|------------------|------------|-------------------------|-------|
|                                   | non faite    | mauvaise qualité | disponible |                         |       |
| Aucun                             | 1018         | 6                | 15         | 17                      | 1056  |
| Tubes citratés                    | 112          | 14               | 49         | 88                      | 239   |
| Tubes secs et EDTA                | 287          | 8                | 42         | 63                      | 400   |
| Total                             | 1417         | 28               | 76         | 168                     | 1689  |

Table 1. S'agissant d'un registre bicentrique, les données biologiques et d'imagerie ne sont pas disponibles pour tous les patients. Les caractéristiques de la population générale, du sous-groupe des patients ayant eu l'échocardiographie initiale et celle de suivi ainsi que le sous-groupe de patients ayant eu ces deux échocardiographies et un prélèvement sanguin sur tubes EDTA et tubes sec sont présentés dans la Table 2. Dans le sous-groupe de patients ayant eu la seconde échocardiographie dans notre centre, le délai médian de suivi était de 219 jours (espace interquartile : 182 – 228 jours).

Les travaux originaux détaillés dans la suite de ce document proviennent donc de l'exploitation des données prospectivement acquises dans le cadre du registre RESIST.

Table 2 : Caractéristiques de la population incluse dans le registre RESIST.

|                                       | Population<br>générale | Patients<br>vivants<br>à 3 mois | Sous-groupe<br>avec ETT<br>complètes | valeur<br>de p* | Sous-groupe<br>avec biologie<br>disponible | valeur<br>de p <sup>†</sup> |
|---------------------------------------|------------------------|---------------------------------|--------------------------------------|-----------------|--------------------------------------------|-----------------------------|
|                                       | n=1865                 | n=1689                          | n=168                                |                 | n=63                                       |                             |
| Age, années                           | 63,6 [53,5 – 73,7]     | 63,7 [53,6 – 73,8]              | 64,6 [54,5 – 72,4]                   | 0,73            | 65,8 [54,5 – 72,0]                         | 1                           |
| Sexe masculin                         | 1389 (74,4%)           | 1268 (75,1%)                    | 137 (81,5%)                          | 0,051           | 52 (82,5%)                                 | 0,22                        |
| Hypertension artérielle               | 795 (42,6%)            | 691 (40,9%)                     | 62 (36,9%)                           | 0,31            | 23 (36,5%)                                 | 0,56                        |
| Tabagisme                             | 943 (50,5%)            | 879 (52,0%)                     | 98 (58,3%)                           | 0,11            | 37 (58,7%)                                 | 0,34                        |
| Diabète de type 2                     | 220 (11,8%)            | 186 (11,0%)                     | 22 (13,1%)                           | 0,44            | 10 (15,9%)                                 | 0,30                        |
| ATCD fam. cardio-vasc.                | 405 (21,7%)            | 388 (23,0%)                     | 34 (20,2%)                           | 0,43            | 15 (23,8%)                                 | 1                           |
| Hypercholestérolémie                  | 675 (36,2%)            | 607 (35,9%)                     | 65 (38,7%)                           | 0,49            | 29 (46,0%)                                 | 0,12                        |
| IMC, kg/m <sup>2</sup>                | 26,3 [24,2 – 29,1]     | 26,3 [24,2 – 29,1]              | 26,1 [23,8 – 29,1]                   | 0,44            | 26,5 [23,8 – 29,4]                         | 0,55                        |
| Infarctus antérieur                   | 679 (36,4%)            | 596 (35,3%)                     | 69 (41,1%)                           | 0,12            | 23 (36,5%)                                 | 0,95                        |
| Délai ECG qualifiant, h               | 1,8 [1,0 – 3,7]        | 1,8 [1,0 – 3,6]                 | 1,8 [1,0 – 3,2]                      | 0,68            | 1,9 [1,1 – 4,6]                            | 0,32                        |
| <i>A l'admission</i>                  |                        |                                 |                                      |                 |                                            |                             |
| FC, bpm (n=1666)                      | 74 [62 – 87]           | 74 [62 – 86]                    | 73 [63 – 88]                         | 0,81            | 76 [66 – 89]                               | 0,20                        |
| PAS, mmHg (n=1644)                    | 140 [120 – 160]        | 140 [122 – 160]                 | 140 [120 – 155]                      | 0,19            | 145 [123 – 158]                            | 0,89                        |
| PAD, mmHg (n=1638)                    | 81 [70 – 94]           | 82 [72 – 95]                    | 80 [70 – 94]                         | 0,36            | 86 [70 – 96]                               | 0,85                        |
| <i>Stratégie de reperfusion</i>       |                        |                                 |                                      |                 |                                            |                             |
| Fibrinolyse réalisée (n=1799)         | 240 (13,3%)            | 213 (12,2%)                     | 19 (11,4%)                           | 0,55            | 2 (3,2%)                                   | 0,02                        |
| Succès                                | 116 (48,3%)            | 104 (48,8%)                     | 14 (77,8%)                           | 0,03            | 2 (100,0%)                                 | 0,24                        |
| Artère coupable (n=1785)              |                        |                                 |                                      | 0,59            |                                            | 0,29                        |
| Tronc commun                          | 17 (0,9%)              | 17 (1,1%)                       | 0                                    |                 | 0                                          |                             |
| IVA                                   | 757 (42,4%)            | 691 (42,9%)                     | 74 (44,6%)                           |                 | 32 (50,8%)                                 |                             |
| Circonflexe                           | 275 (15,4%)            | 250 (15,5%)                     | 21 (12,7%)                           |                 | 6 (9,5%)                                   |                             |
| Coronaire droite                      | 722 (40,4%)            | 646 (40,1%)                     | 70 (42,2%)                           |                 | 24 (38,1%)                                 |                             |
| Pontage aorto-coronaire               | 4 (0,2%)               | 3 (0,2%)                        | 0                                    |                 | 0                                          |                             |
| Pas de lésion coronaire               | 10 (0,6%)              | 5 (0,3%)                        | 1 (0,6%)                             |                 | 1 (1,6%)                                   |                             |
| Non précisé                           | 80                     | 77                              | 2                                    |                 | 0                                          |                             |
| Angioplastie (n=1758)                 | 1586 (90,2%)           | 1437 (90,7%)                    | 145 (90,1%)                          | 0,78            | 58 (93,5%)                                 | 0,66                        |
| Obtention flux TIMI3 (n=1604)         | 1503 (93,7%)           | 1401 (95,2%)                    | 148 (96,7%)                          | 0,66            | 56 (96,6%)                                 | 1                           |
| Délai → TIMI3, h <sup>‡</sup> (n=995) | 4,3 [2,9 – 6,8]        | 4,2 [2,8 – 6,7]                 | 4,4 [3,0 – 6,7]                      | 0,36            | 4,1 [2,7 – 6,3]                            | 0,48                        |

L'exhaustivité des données étant très variable d'un patient à l'autre, nous présentons ici les caractéristiques de la population générale, du sous-groupe de patients ayant eu les deux échocardiographies (initiale et de suivi) complètes (en bleu). Les caractéristiques de ces patients qui ont eu également un prélèvement sanguin sur tube EDTA et sur tube sec sont aussi présentées (en vert). Les données sont présentées sous forme de médiane et d'espace interquartile ou nombre (pourcentage). FC, fréquence cardiaque ; PAD, pression artérielle diastolique ; PAS, pression artérielle systolique. \*Comparaison par rapport au reste de la population des patients vivants à 3 mois (n=1521 patients).  
<sup>†</sup> Comparaison par rapport au reste de la population des patients vivants à 3 mois (n=1626 patients). <sup>‡</sup> Délai entre le début de la douleur et l'obtention d'un flux TIMI3 en coronarographie. La coronarographie étant différée en cas de succès de fibrinolyse, ces patients ne sont pas comptabilisés ici.

# **Axe imagerie du remodelage ventriculaire gauche en post-infarctus**

## **Définition du remodelage ventriculaire gauche en IRM : revue de la littérature**

Le RVG est fréquemment décrit dans la littérature comme un facteur de mauvais pronostic après un STEMI [6–8]. Pourtant, il n'existe pas de recommandation sur la modalité d'imagerie, le délai de réalisation de l'imagerie ou encore les valeurs seuils d'augmentation des volumes ventriculaires gauches à utiliser. L'échocardiographie et l'IRM sont les deux principales modalités d'imagerie utilisées pour quantifier l'évolution des volumes au décours d'un STEMI et donc pour affirmer l'existence d'un RVG. L'IRM possède une meilleure reproductibilité de la mesure des volumes ventriculaires [54] et nous nous sommes donc limités dans ce travail aux études ayant utilisé l'IRM pour la quantification des volumes VG. Nous avons donc recherché de façon exhaustive les études publiées dans les 10 dernières années ayant évalué la prévalence d'un RVG, au moyen de l'IRM, au décours d'un STEMI.

Entre janvier 2010 et août 2019, nous avons retrouvé 77 publications étudiant le RVG en IRM au décours d'un STEMI. Certaines cohortes ayant fait l'objet de plusieurs publications, nous avons retenu pour chaque cohorte la publication qui présente l'effectif le plus grand. Parmi les 37 publications retenues, 30 utilisent une valeur seuil pour définir le RVG (les autres le définissent comme une variable continue). La prévalence du RVG varie de 11,3 à

48,4% dans les études ayant utilisé une valeur seuil de définition du RVG (prévalence groupée de 22,8% [19,4% – 26,7%] dans la méta-analyse,  $I^2=84\%$ ). Les valeurs seuil de 20% et 15% d'augmentation des volumes VG sont les plus fréquemment retrouvées (respectivement dans 13 (35%) et 9 (24%) des études). Les définitions les plus fréquemment utilisées sont (i) une augmentation  $\geq 20\%$  du volume télédiastolique VG (indexé ou non), évalué 3 à 5 mois après le SCA (5 études, 638 patients, prévalence groupée du RVG: 18,8% [16,0% – 22,1%],  $I^2=0\%$ ), (ii) une augmentation  $\geq 15\%$  du volume télésystolique VG (indexé ou non), évalué 3 à 5 mois après le SCA (3 études, 224 patients, prévalence groupée du RVG: 23,7% [18,2% – 30,2%],  $I^2=9\%$ ) et, (iii) une augmentation  $\geq 20\%$  du volume télédiastolique VG (indexé ou non), évalué 6 mois après le SCA (4 études, 676 patients, prévalence groupée du RVG: 17,0% [12,1% – 23,5%],  $I^2=70\%$ ).

Cette revue a montré la grande hétérogénéité concernant la définition du RVG dans les études ayant utilisé l'IRM comme modalité d'imagerie, au décours d'un STEMI. De plus, les patients inclus dans ces études sont fréquemment sélectionnés et ne reflètent pas l'ensemble des patients qui présentent un STEMI. L'utilisation d'une unique mesure de volume (télédiastolique ou télésystolique) ne permet pas d'appréhender la fonction cardiaque. Une définition combinant les variations du volume télédiastolique et du volume télésystolique permet de faire la différence entre une situation où seul le volume télédiastolique est augmenté (et donc où la FEVG s'améliore) et une augmentation conjointe des volumes télédiastolique et télésystolique, pouvant s'accompagner d'une dégradation de la FEVG dans le suivi. Prenant en compte la reproductibilité des mesures en IRM, il serait pertinent d'étudier la valeur pronostique d'un RVG qui serait défini par une augmentation du volume télédiastolique de 12 à 20% associé à une augmentation du volume télésystolique de 12 à 15% dans une population

non sélectionnée de patients présentant un STEMI. Le délai de réalisation de 3 mois permet de dépister précocement les patients qui présentent un RVG, permettant ainsi d'optimiser au plus tôt leur prise en charge.

**Legallois D**, Hodzic A, Alexandre J, Dolladille C, Saloux É, Manrique A, Roule V, Labombarda F, Milliez P, Beygui F.

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## Definition of left ventricular remodelling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade

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### Abstract

An increase in left ventricular volumes between baseline and follow-up imaging is the main criteria for the quantification of left ventricular remodelling (LVR) after ST-elevation myocardial infarction (STEMI), but without consensual definition. We aimed to review the criteria used for the definition of LVR based on cardiac magnetic resonance imaging (CMR) in STEMI patients. A systematic literature search was conducted using MEDLINE and the Cochrane Library from January 2010 to August 2019. Thirty-seven studies involving 4209 patients were included. Among these studies, 30 (81%) used a cut-off value for defining LVR, with a pooled LVR prevalence estimate of 22.8%, 95% CI [19.4–26.7%] and a major between-study heterogeneity ( $I^2 = 82\%$ ). The seven remaining studies (19%) defined LVR as a continuous variable. The definition of LVR using CMR following STEMI is highly variable, among studies including highly selected patients. A 20% increase or a 15% increase in left ventricular volumes between a baseline and a follow-up CMR imaging were the two most common criterion (13 [35%] and 9 [24%] studies, respectively). The most frequent LVR criterion was a 20% increase in end-diastolic volumes or a 15% increase in end-systolic volumes. A composite cut-off value of a 12 to 15% increase in end-systolic volume and a 12 to 20% increase in end-diastolic volume using a follow-up CMR imaging 3 months after STEMI might be proposed as a consensual cut-off for defining adverse LVR for future large-sized, prospective studies with serial CMR imaging and long-term follow-up in unselected patients.

**Keywords** ST-elevation myocardial infarction · Left ventricular remodelling · Cardiac magnetic resonance

### Introduction

Cardiac remodelling may be defined as changes in genome expression resulting in molecular, cellular and interstitial changes, leading to changes in the size, shape and function of the heart and vasculature [1]. After

acute myocardial infarction, inflammatory responses and neuroendocrine activation lead to the replacement of dead cardiomyocytes by a fibrotic scar. Left ventricular (LV) dilation and remodelling occur later due to myocyte hypertrophy, interstitial fibrosis and enhanced haemodynamic burden [2].

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s10741-020-09975-3>) contains supplementary material, which is available to authorized users.

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Left ventricular remodelling (LVR) is associated with poor outcome in patients with acute myocardial infarction [3]. Hence, the assessment of LVR is of major importance since reversing, stopping or at least delaying remodelling is the goal of therapy in heart failure. However, there is no consensual definition of LVR after ST-elevation myocardial infarction (STEMI). An increase in LV volumes (end-diastolic volume (EDV) or end-systolic volume (ESV)) between baseline and follow-up imaging is the main criteria for the quantification of LVR, but the wide range of cut-offs used and the variable timing of imaging may contribute to the heterogeneity of results between studies and highlights the need for a uniform definition.

Cardiac magnetic resonance (CMR) imaging provides an accurate and reproducible assessment of global and regional LV function and allows for quantification of fibrosis [4]. A 20% increase in LV volumes has been used for the definition of LVR, but this cut-off was initially proposed in echocardiographic studies prior to the era of primary percutaneous coronary intervention (PPCI) [5]. However, even when using CMR, the criteria for cardiac remodelling remain controversial.

In the present work, we aimed to review the criteria used for the definition of LVR based on CMR imaging in studies including patients with STEMI.

## Methods

### Data sources and searches

We performed a systematic search in online literature databases (PubMed/MEDLINE and Cochrane Library, see [Online Resource](#)) for articles published between January 2010 and August 2019 that reported on LV remodelling and/or LV volumes using CMR imaging in STEMI patients. Studies before 2010 were not included, as recent developments in the management of STEMI (e.g. use of more potent P2Y12 inhibitors, wider use of PPCI) have led to significant changes in outcomes and adding older studies may lead to a cumbersome analysis. In addition, we searched the references of the articles identified to find other suitable studies. Only peer-reviewed and published studies were included. Authors were not contacted for additional information not included in the published papers.

### Study selection

Eligible studies had to fulfil the following criteria: (i) patients were admitted with STEMI, (ii) a definition of LVR was given, (iii) the baseline CMR assessment was performed within 10 days following STEMI, (iv) the number of included patients was  $\geq 30$ , (v) the time interval between the baseline and follow-up was  $\geq 1$  month and (vi) the article was written in English. Special attention was taken to exclude duplicate

patient populations. The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines ([Online Resource](#)). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42018114977.

### Data extraction and quality assessment

All data were independently extracted from the full reports by two investigators (DL and AH). Discrepancies were solved by consensus. The assessment of the quality of included randomized controlled trials was realized using the Cochrane Collaboration's tool for assessing the risk of bias [6]. Based on the evaluation, studies were classified into low, unclear, or high risk of bias. For the assessment of the quality of included non-interventional studies, we used the modified version of the Newcastle-Ottawa Scale [7] in order to account for concepts relevant to LVR that may bias study results or comparability. Non-interventional studies were judged to be at low ( $\geq 3$  points) or high risk of bias ( $< 3$  points).

### Data synthesis and analysis

Studies were classified according to (i) LVR criteria and (ii) the time between the two CMR imaging sessions (3 to 5 months, 6 months or 7 to 12 months). In these subgroups, LVR prevalence among patients with STEMI was calculated by pooling the estimated prevalence of each study using a random effects meta-analysis that accounted for between-study heterogeneity. Binomial prevalence and 95% confidence intervals (95% CI) for individual studies were calculated using the Clopper-Pearson method. We assessed between-study heterogeneity using standard  $\chi^2$  tests (significant if  $p < 0.10$ ) and the  $I^2$  statistic ( $> 50\%$  was considered as significant heterogeneity) in subgroup analysis. Sensitivity analysis of the pooled prevalence estimate was performed by excluding each study sequentially from the calculation. Bias secondary to the study's size effects was investigated by funnel plot and Egger test. Figures and analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were two-sided and used a significance threshold of  $p < 0.05$ .

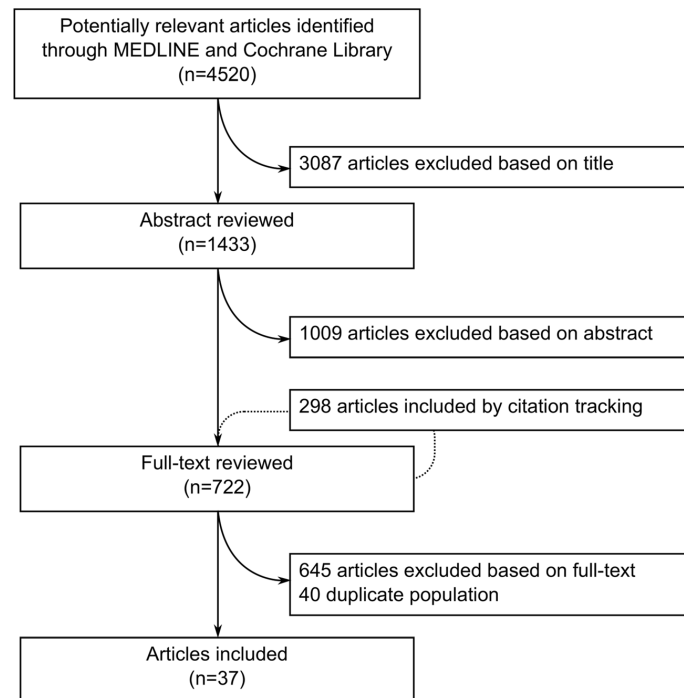
## Results

### Literature search

The initial literature search yielded 4520 potentially relevant references, of which 3087 articles were excluded based on the title and 1009 after reading the abstract (Fig. 1). Citation tracking identified an additional 298 articles. A full-text review was

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**Fig. 1** Flowchart of studies reviewed and included

completed on the 722 remaining articles and 37 studies met our inclusion criteria.

### Study and population characteristics

Thirty-seven studies involving 4209 patients were included [8–44]. The characteristics of the included studies are depicted in Table 1 and Online Resource. The median number of patients per study was 72 (range 31–383). Twelve (32%, 1256 patients) were part of a randomized clinical trial; 22 studies were prospectively recruited longitudinal studies, and the remaining 3 studies were retrospective or from registries. The median follow-up duration was 6 months (range, 3–12), and the second CMR session was performed at 6 months in 14 studies (38%). The median patient age was 59 years [inter-quartile range, 57.5–60.5], and 82% were male. Fifty percent of the patients had anterior STEMI and/or the left anterior descending artery as the culprit vessel. PPCI was an inclusion criterion in 24 studies, and 93% of the overall population underwent PPCI. Almost all the remaining patients had fibrinolysis with either success or rescue PCI.

### Cardiac magnetic resonance imaging data

Paired EDV and ESV (indexed on body surface area or not) and LV ejection fraction (LVEF) were available in 29, 26 and

31 studies, respectively (Fig. 2 and Online Resource). Mean or median EDV at baseline ranged from 117 to 183 mL (median, 146 mL), indexed EDV ranged from 64.5 to 93.0 mL/m<sup>2</sup> (median, 79.7 mL/m<sup>2</sup>), ESV ranged from 57 to 94 mL (median, 68 mL) and indexed ESV ranged from 33.6 to 53.5 mL/m<sup>2</sup> (median, 42 mL/m<sup>2</sup>). Mean or median LVEF at baseline ranged from 40 to 58% (median, 48.6%). Mean or median EDV or EDVI increased in 26/29 studies and mean or median ESV or ESI decreased in 17/26 studies between the two CMR imaging sessions. As a consequence, mean or median LVEF improved in 30/31 studies between baseline and follow-up CMR imaging.

### Definition of LVR

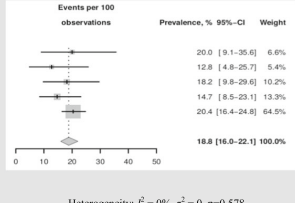
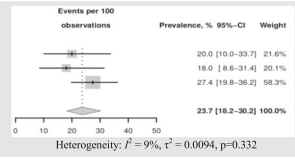
Thirty studies (81%) used a cut-off value for LVR (Table 1 and Online Resource), and 7 (19%) defined LVR as a continuous variable. When LVR was defined as dichotomous criteria, the prevalence of LVR ranged from 11.3 to 48.4%. Meta-analysis showed a pooled LVR prevalence of 22.8%, 95% CI [19.4–26.7%], (Fig. 3, 28 studies [8–35]) with significant between-study heterogeneity ( $I^2 = 82\%$ ). No individual study affected the overall prevalence estimate by more than 1% (Online Resource). The cut-off values of 20% and 15% increases in LV volumes were the two most common criteria (13 [35%] and 9 [24%] studies, respectively). Twenty-nine

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**Table 1** Main characteristics of the studies included in this systematic review. Subgroup meta-analysis of the prevalence of LVR among patients presenting with STEMI using CMR imaging. Further data are available in [Online Resource](#). CMR, cardiac magnetic resonance; EDV, end-

diastolic volume; EDVI, end-diastolic volume index; ESV, end-systolic volume; ESVI, end-systolic volume index; LVR, left ventricular remodeling; RCT, randomized clinical trial

| First author, year                                  | Sample size | Design                     | Timing of the follow-up CMR | Definition of LVR                  | Patients with LVR | Meta-analytic pooling of LVR prevalence, Proportion, 95%-CI, Weight<br>(only if there is ≥ 3 studies with similar characteristics) |
|-----------------------------------------------------|-------------|----------------------------|-----------------------------|------------------------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>Follow-up CMR imaging session: 3 to 5 months</b> |             |                            |                             |                                    |                   |                                                                                                                                    |
| <i>EDV-based criteria</i>                           |             |                            |                             |                                    |                   |                                                                                                                                    |
| Biesbroek, 2017                                     | 42          | Prospective study          | 3 months                    | ΔEDV ≥ 15%                         | 8 (19%)           |                                                  |
| Bulluck, 2016                                       | 40          | Prospective                | 5 months                    | ΔEDV ≥ 20%                         | 8 (20%)           |                                                                                                                                    |
| Reinstadler, 2013                                   | 47          | Prospective                | 4 months                    | ΔEDV ≥ 20%                         | 6 (12.8%)         |                                                                                                                                    |
| Pokorney, 2012                                      | 66          | Prospective                | 4 months                    | ΔEDVI > 20%                        | 12 (18.2%)        |                                                                                                                                    |
| Reindl, 2018                                        | 102         | Prospective                | 4 months                    | ΔEDV ≥ 20%                         | 15 (14.7%)        |                                                                                                                                    |
| Symons, 2016                                        | 383         | Prospective                | 4 months                    | ΔEDV > 20%                         | 78 (20.4%)        |                                                                                                                                    |
| Shetelig, 2018                                      | 240         | Post-hoc analysis of a RCT | 4 months                    | increase EDVI ≥ 10mL/m2            | not available     |                                                                                                                                    |
| Wong, 2013                                          | 64          | Prospective                | 3 months                    | ΔEDV                               | NA                |                                                                                                                                    |
| <i>ESV-based criteria</i>                           |             |                            |                             |                                    |                   |                                                                                                                                    |
| Garg, 2017                                          | 50          | Prospective                | 3 months                    | ΔESV > 15%                         | 10 (20%)          |                                                 |
| Van Melle, 2010                                     | 50          | Prospective                | 4 months                    | ΔESV ≥ 15%                         | 9 (18%)           |                                                                                                                                    |
| Gerbaud, 2014                                       | 124         | Prospective                | 3 months                    | ΔESV ≥ 15%                         | 34 (27.4%)        |                                                                                                                                    |
| <i>Composite criteria</i>                           |             |                            |                             |                                    |                   |                                                                                                                                    |
| Shetye, 2017                                        | 65          | Prospective                | 4 months                    | ΔESVI ≥ 15% or ΔEDVI ≥ 20%         | 11 (16.9%)        |                                                                                                                                    |
| Hallen, 2010                                        | 132         | Post-hoc analysis of a RCT | 4 months                    | ΔESVI and ΔEDVI                    | NA                |                                                                                                                                    |
| Janssens, 2018                                      | 197         | RCT                        | 4 months                    | ΔESV and ΔEDV and sphericity index | NA                |                                                                                                                                    |
| Najjar, 2011                                        | 124         | RCT                        | 3 months                    | EDVI, ESVI and LV mass index       | NA                |                                                                                                                                    |

studies (78%) used EDV or EDVI to define LVR and 15 studies (41%) used ESV or ESVI. Seven studies used both end-diastolic and end-systolic LV volumes. Other criteria, including LV mass index [40] or sphericity index [39], were described. Three remodelling criteria were used in  $\geq 3$  studies: (i) a  $\geq 20\%$  increase in EDV or EDVI at 3 to 5 months (5 studies, 638 patients; prevalence of LVR, 18.8%; 95% CI [16.0–22.1%];  $I^2 = 0\%$ ), (ii) a  $\geq 15\%$  increase in ESV or ESVI at 3 to 5 months (3 studies, 224 patients; prevalence of LVR, 23.7%; 95% CI [18.2–30.2%];  $I^2 = 9\%$ ) and (iii) a  $\geq 20\%$  increase in EDV or EDVI at 6 months (4 studies, 676 patients; prevalence of LVR, 17.0%; 95% CI [12.1–23.5%]; with significant heterogeneity,  $I^2 = 70\%$ ).

### Risk of bias assessment

Among the 25 non-interventional studies included in this review, 8 (32%) were at high risk of bias (see: [Online Resource](#)). Main biases were a small sample size and the lack of representativeness of the average STEMI patients (e.g. exclusion of patients with low LVEF or clinical signs of heart failure). The risk of bias assessment in each randomized controlled trial is reported in the [Online Resource](#). Most of the trials had a low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment and

selective reporting. Seven trials had a high risk of bias for blinding of participants and personnel, and 4 a high risk of bias in outcome data completion. Funnel plot and Egger tests revealed no asymmetry ( $p = 0.17$ , Fig. 4).

### Discussion

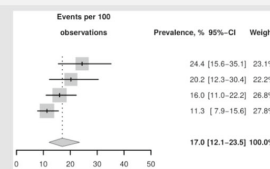
This systematic review highlighted that (i) the definition of LVR using CMR in STEMI patients is highly variable; (ii) an increase of 20% of end-diastolic volumes or an increase of 15% of end-systolic volumes between a baseline and a follow-up CMR imaging  $\leq 6$  months after STEMI is commonly used as a definition of LVR; and (iii) the LVR prevalence estimate is 22.8%, 95% CI [19.4–26.7%], with significant between-study heterogeneity in this highly selected population.

The *International Forum on Cardiac remodelling* held in 1998 led to a consensus paper on the key concepts and definition of LVR [1]. Our review shows that 20 years later, the only consensual point is to describe LVR as a change in LV volumes. The lack of a standard definition has led to major heterogeneity and low-quality publications with subsequent imprecision in drawing conclusions about the definition, the incidence, the correlates and the prognostic value of LVR in the setting of STEMI.

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Table 1 (continued)

| First author, year                                   | Sample size   | Design                     | Timing of the follow-up CMR | Definition of LVR                                               | Patients with LVR | Meta-analytic pooling of LVR prevalence, Proportion, 95%-CI, Weight<br>(only if there is ≥ 3 studies with similar characteristics)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
|------------------------------------------------------|---------------|----------------------------|-----------------------------|-----------------------------------------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|---------------|--------|--------|--------------|------|-------------|-------|-----------------------|------|-------------|-------|------------|------|-------------|-------|---------------------------|------|------------|-------|-----------|------|-------------|--------|
| <b>Follow-up CMR imaging session: 6 months</b>       |               |                            |                             |                                                                 |                   |  <table><thead><tr><th>Study</th><th>Prevalence, %</th><th>95%-CI</th><th>Weight</th></tr></thead><tbody><tr><td>Sugano, 2017</td><td>24.4</td><td>(15.6–35.1)</td><td>23.1%</td></tr><tr><td>Fabregat-Andrés, 2015</td><td>20.2</td><td>(12.3–30.4)</td><td>22.2%</td></tr><tr><td>Mele, 2017</td><td>16.0</td><td>(11.0–22.2)</td><td>26.8%</td></tr><tr><td>Rodríguez-Palomares, 2019</td><td>11.3</td><td>(7.9–15.6)</td><td>27.8%</td></tr><tr><td>Cha, 2019</td><td>17.0</td><td>(12.1–23.5)</td><td>100.0%</td></tr></tbody></table> <p>Heterogeneity: <math>I^2 = 70\%</math>, <math>\tau^2 = 0.1163</math>, <math>p=0.02</math></p> | Study | Prevalence, % | 95%-CI | Weight | Sugano, 2017 | 24.4 | (15.6–35.1) | 23.1% | Fabregat-Andrés, 2015 | 20.2 | (12.3–30.4) | 22.2% | Mele, 2017 | 16.0 | (11.0–22.2) | 26.8% | Rodríguez-Palomares, 2019 | 11.3 | (7.9–15.6) | 27.8% | Cha, 2019 | 17.0 | (12.1–23.5) | 100.0% |
| Study                                                | Prevalence, % | 95%-CI                     | Weight                      |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Sugano, 2017                                         | 24.4          | (15.6–35.1)                | 23.1%                       |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Fabregat-Andrés, 2015                                | 20.2          | (12.3–30.4)                | 22.2%                       |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Mele, 2017                                           | 16.0          | (11.0–22.2)                | 26.8%                       |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Rodríguez-Palomares, 2019                            | 11.3          | (7.9–15.6)                 | 27.8%                       |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Cha, 2019                                            | 17.0          | (12.1–23.5)                | 100.0%                      |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| <i>EDV-based criteria</i>                            |               |                            |                             |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Sugano, 2017                                         | 68            | Prospective                | 6 months                    | $\Delta\text{EDV} > 5\%$                                        | 22 (32%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Fabregat-Andrés, 2015                                | 31            | Prospective                | 6 months                    | $\Delta\text{EDV} > 10\%$                                       | 15 (48%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Mele, 2017                                           | 41            | Retrospective              | 6 months                    | $\Delta\text{EDV} \geq 15\%$                                    | 10 (24%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Rodríguez-Palomares, 2019                            | 374           | Variable                   | 6 months                    | $\Delta\text{EDV} > 15\%$                                       | 105 (28.1%)       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Cha, 2019                                            | 82            | Retrospective              | 6.5 months                  | $\Delta\text{EDV} \geq 20\%$                                    | 20 (24.4%)        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Yoon, 2013                                           | 84            | RCT                        | 6 months                    | $\Delta\text{EDV} > 20\%$                                       | 17 (20.2%)        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Caldentey, 2017                                      | 227           | Prospective                | 6 months                    | $\Delta\text{EDV} \geq 20\%$                                    | 29 (16.0%)        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Carberry, 2017                                       | 283           | Prospective                | 6 months                    | $\Delta\text{EDV} \geq 20\%$                                    | 32 (11.3%)        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Huttin, 2017                                         | 121           | Prospective                | 6 months                    | $\Delta\text{EDV} > 17.3\text{mL}$                              | 36 (29.8)         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Grabmaier, 2017                                      | 44            | Post-hoc analysis of a RCT | 6 months                    | $\Delta\text{EDV}$                                              | NA                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| <i>ESV-based criteria</i>                            |               |                            |                             |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Eitel, 2011                                          | 112           | RCT                        | 6 months                    | $\Delta\text{ESVI} > 0\%$                                       | 51 (45.5%)        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Watabe, 2016                                         | 92            | Prospective                | 6 months                    | $\Delta\text{ESV} > 0\%$                                        | 29 (32%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Husser, 2013                                         | 234           | Prospective                | 6 months                    | dilated ESVI (reference values)                                 | 94 (40%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| <i>Composite criteria</i>                            |               |                            |                             |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Traverse, 2010                                       | 40            | RCT                        | 6 months                    | $\Delta\text{ESV}$ and $\Delta\text{EDV}$                       | NA                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Achilli, 2014                                        | 35            | RCT                        | 6 months                    | $\Delta\text{EDV} > 20\text{mL}$ or $\Delta\text{LVEF} > 5\%$   | not available     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| <b>Follow-up CMR imaging session: 7 to 12 months</b> |               |                            |                             |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| <i>EDV-based criteria</i>                            |               |                            |                             |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Tanimoto, 2010                                       | 104           | Prospective                | 8 months                    | $\Delta\text{EDV} > 15\%$                                       | 21 (20%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| O'Regan, 2012                                        | 46            | Prospective                | 12 months                   | $\Delta\text{EDV} \geq 20\%$                                    | 16 (35%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Gobbara, 2015                                        | 69            | Prospective                | 7 months                    | $\Delta\text{EDVI} \geq 20\%$                                   | 18 (26%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| <i>ESV-based criteria</i>                            |               |                            |                             |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Garcia, 2019                                         | 192           | Prospective                | 12 months                   | $\Delta\text{ESV} \geq 10\%$                                    | 32 (16.7%)        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Sörensson, 2013                                      | 68            | Post-hoc analysis of a RCT | 12 months                   | $\Delta\text{ESV} \geq 15\%$                                    | 9 (13%)           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| <i>Composite criteria</i>                            |               |                            |                             |                                                                 |                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Mangion, 2016                                        | 72            | Post-hoc analysis of a RCT | 7 months                    | $\Delta\text{ESVI} \geq 20\%$ and $\Delta\text{EDVI} \geq 20\%$ | 11 (13%)          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |
| Sürder, 2016                                         | 150           | Post-hoc analysis of a RCT | 12 months                   | $\Delta\text{EDV}$ , $\Delta\text{ESV}$                         | NA                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |               |        |        |              |      |             |       |                       |      |             |       |            |      |             |       |                           |      |            |       |           |      |             |        |

### Patient's characteristics in CMR studies

The selected patients included in the CMR studies were relatively young (mean or median age, 59 years), had a preserved LVEF (median, 48.6%) and mostly underwent PPCI (93%). The reported rate of PPCI increased over time [45]. However, in the FAST-MI 2015 registry, the non-selected patients were older ( $63 \pm 14$  years), and only 71% underwent primary PCI [46]. In addition, 28% of the patients we included in the present review were included as part of a randomized clinical trial and very few studies enrolled consecutive STEMI patients. As a consequence, patients with heart failure or low kidney function were mostly excluded. Additionally, there was a low incidence of major adverse cardiovascular events (MACE) during follow-up, in line with the baseline LVEF. Hence, the patients included in CMR studies after STEMI were highly selected, questioning the extrapolation of their conclusions to non-selected STEMI patients.

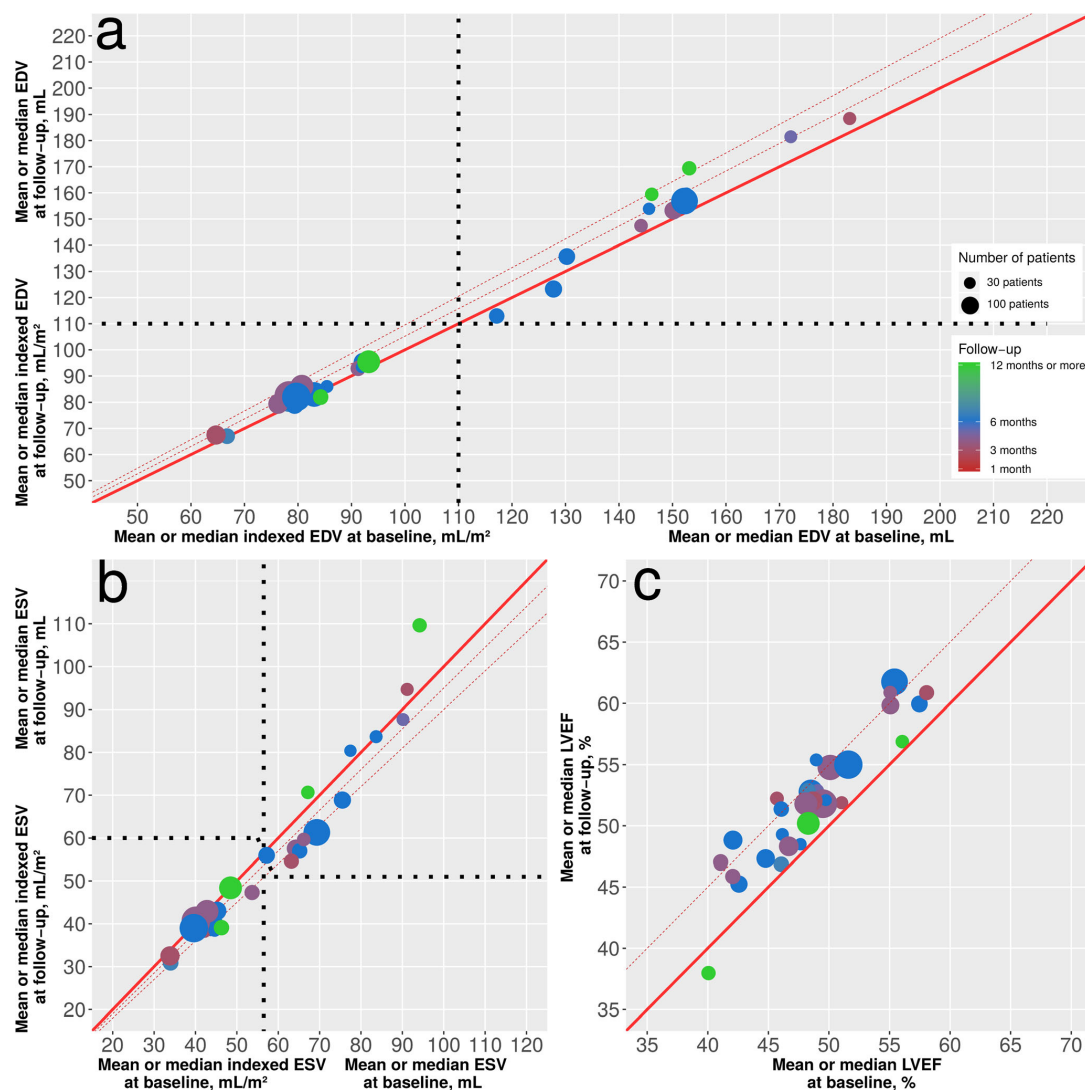
### Definition of the optimal cut-off value for LV volume increase

When defined, the cut-off value of a 15% increase in ESV or a 20% increase in EDV remains the most frequent criterion for LVR in CMR studies. An ideal threshold value for the volume variation has to be (i) wide enough to be beyond the test-retest repeatability of the assessment method, (ii) predictive of outcomes, hence leading to significant changes in the management of patients and (iii) reproducible among studies.

Most of the studies assessing the prognostic value of LVR following STEMI used echocardiography and were conducted > 15 years ago, prior to the era of PPCI [5]. A 20% increase in LV volumes, based on the upper limit of the 95% CI of the intra-observer variability for  $\Delta\text{EDV}$ , has been widely used to define LVR [5]. The assessment of global and regional LV function using CMR is more accurate than TTE because of its 3D analysis, higher spatial resolution and superior intra-observer variability [4,

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**Fig. 2** End-diastolic volumes (a), end-systolic volumes (b) and LVEF (c) at baseline and during follow-up in studies with CMR paired data. Indexed LV volumes are depicted in the left lower corner of the plots, whereas non-indexed volumes are depicted in the upper right corner. Each study is represented once per plot. The area of each circle is related to the sample size of the study. The bold red line represents the identity

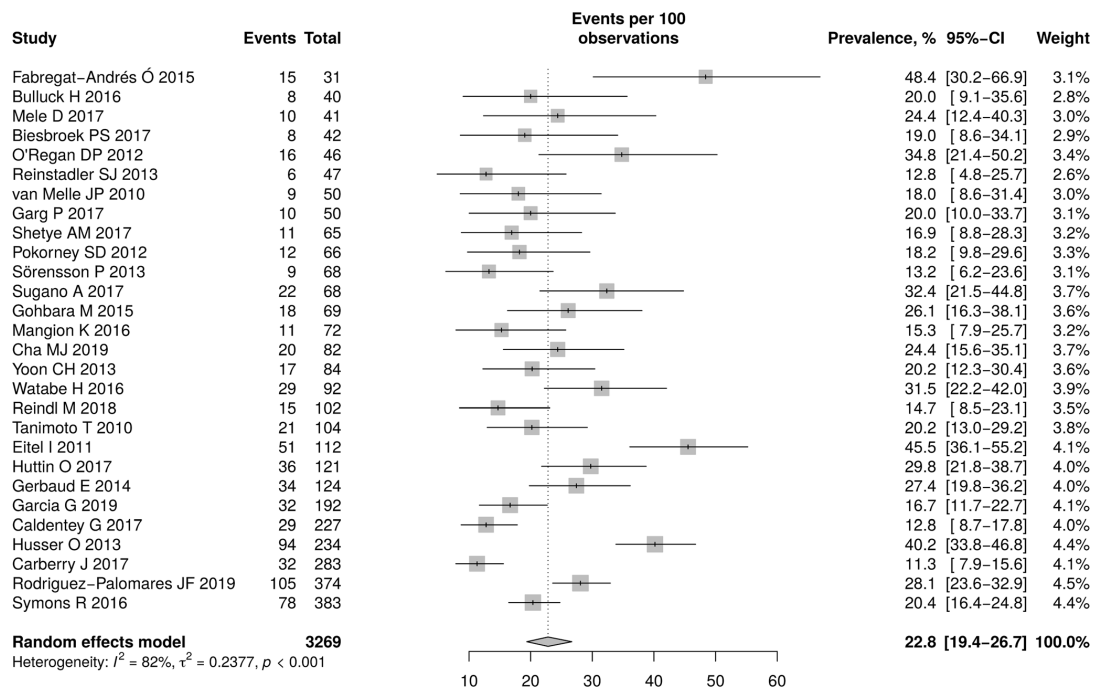
line where volumes or LVEF is identical between baseline and follow-up. The two dotted lines show a 5% and a 10% increase in mean EDV or indexed EDV during the course of follow-up (panel a). The two dotted lines show a 5% and a 10% decrease in mean ESV or indexed ESV during follow-up (panel b). The dotted line in panel c shows an absolute improvement of 5% on LVEF between baseline and follow-up

[47]. It remains unclear whether investigators should use EDV or ESV to define LVR. EDV reflects structural remodelling and preload, whereas ESV is influenced by both loading conditions and fibre shortening [1]. The recent studies that defined LVR using a prognostic-based approach may help to answer this question.

Only a few studies assessed the long-term outcomes associated with LVR, as the follow-up period mostly ended with the second CMR. When available, the event rates were too low to draw any conclusions ([Online Resource](#)). Recently, some studies suggested to define LVR using a prognostic-based approach. Reindl et al. [48] reported that

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**Fig. 3** Meta-analysis of the prevalence of left ventricular remodelling among patients presenting with STEMI using CMR imaging. The square area is proportional to the inverse variance of the estimate

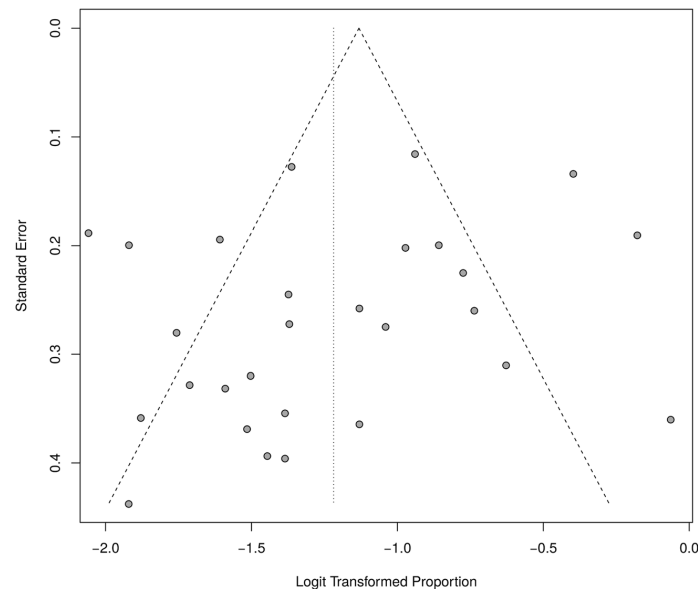
a 10% increase in EDV showed the strongest association with clinical outcomes in 224 patients with STEMI. However, the event-rate was low (13 patients [6%] after a 24-month follow-up). Two recent studies concluded that the follow-up CMR imaging did not add prognostic information upon baseline data, including baseline CMR imaging [34, 49]. Rodríguez-Palomares et al. [34] compiled 374 STEMI patients who had both a baseline and a 6-month CMR imaging. Forty-nine patients presented with the primary endpoint (cardiovascular mortality, hospitalization for HF or ventricular arrhythmia) during a mean follow-up of  $72.9 \pm 42.8$  months. The authors stated that adding remodelling criteria defined as a  $> 15\%$  increase in EDV and a  $> 3\%$  decrease in LVEF did not add prognostic value to a model including only baseline CMR data. However, the population of the latter study differ significantly from actual routine STEMI patients because a subset of patients was included  $> 15$  years ago. Two-thirds of patients had percutaneous coronary intervention  $< 12$  h, only 82% were treated with beta-blockers and  $< 80\%$  with renin-angiotensin-aldosterone system (RAAS) inhibitors at follow-up. Furthermore, the LVEF cut-off suffers from reproducibility issues as it has been demonstrated that the detection of a 3% change in LVEF would require 14 normal subjects or 7 HF patients using CMR imaging [47].

Masci et al. [49] included 492 STEMI patients with both a baseline and a follow-up CMR (median, 4.8 months). Eighty-four patients presented with the primary endpoint (composite of all-death and HF hospitalization), during a mean follow-up of 8.3 years. Both a 20% increase in EDV and a 15% increase in ESV failed to independently predict the primary endpoint. Furthermore, early- (baseline CMR only), deferred- (follow-up CMR only) or repeated-CMR strategies were equivalent for outcome prediction. These results may be interpreted with caution. First, these studies retrospectively compiled databases of previous studies including highly selected patients. Second, the imaging session was performed  $6.2 \pm 2.6$  days [34] and 3 to 6 days (IQR) [49] following STEMI. The baseline CMR imaging is able to quantify infarct size and microvascular obstruction and to improve risk stratification in addition to clinical parameters [50, 51]. Many studies have demonstrated a correlation between infarct size at baseline and LVR, LVEF and infarct size during follow-up. Infarct size is independent of LV volumes, function and loading. However, the assessment of infarct size using CMR has some pitfalls. Infarct size may be overestimated because of inflammatory reactions and it has been demonstrated that there is significant heterogeneity in its assessment using CMR [52, 53]. Also, reversible LV dysfunction

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**Fig. 4** Funnel plot of standard error by logit transformed proportion of LVR to evaluate publication bias for the prevalence of LVR following STEMI. Egger test:  $p = 0.17$



and dilation may be consequences of myocardial stunning. Hence, the first CMR imaging assessing LV volumes and function as well as infarct size may not be performed during the initial week following STEMI, before the end of the stunning time frame and the relative regression of inflammation and oedema [52]. Third, recent data support the usefulness of anti-remodelling drugs following STEMI. A pooled analysis of two large randomized trials demonstrated the benefit of mineralocorticoid receptor antagonists in STEMI (reduction in death and resuscitated sudden death), regardless the existence of heart failure in 2241 patients [54], although LV volumes were not serially assessed.

The definition of LVR states that several mechanisms result in changes in the size, shape and function of the heart and vasculature [1]. The assessment of a single LV volume (either EDV or ESV) does not provide data about LV function. Several CMR studies used a composite definition of LVR, using both EDV and ESV or both EDV and LVEF (Table 1). Bulluck et al. combined the percentage increase in EDV and the percentage increase in ESV for defining different patterns of LVR [55]. A significant increase in EDV may not have the same value whether it is associated with no change in ESV and an increase in LVEF or with a significant increase in ESV with no change or a decrease in LVEF. Previous studies did not evaluate the prognostic value of this combined approach (size, shape and function) for defining LVR. Finally, the present study shows that between-study heterogeneity is low among studies using a follow-up CMR imaging < 6 months and a cut-off value of 15% for ESV and

20% for EDV. Recently, both intra-observer and inter-observer variability were measured in reperfused STEMI patients [55]. Because the minimal detectable change for both EDV and ESV using CMR imaging in STEMI patients was 12% [55], a combine cut-off value of a 12 to 15% increase in ESV and a 12 to 20% increase in EDV might be considered as the most adequate definition of the pattern of adverse LVR following STEMI.

#### Timing of the follow-up CMR imaging

The timing of the second assessment of LV volumes is also a matter of debate. Identifying LVR early after STEMI may have clinical implications leading to actions to prevent its detrimental effects. However, serial CMR imaging after STEMI showed that LV volumes remained stable during the first month and that ESV decreased significantly at 3 months, leading to a significant improvement in LVEF between 1 and 3 months [56]. Hence, it seems reasonable to perform the follow-up CMR 3 months after STEMI to be able to detect early LVR and potentially allowing the uptitration of antiremodelling drugs.

#### Limitations

Our study has some limitations that should be acknowledged. First, we chose to include only articles published after 2010 as in older studies the standard of care for STEMI was different. Second, we only included studies using CMR and not

echocardiography. Third, we did not discuss the even more controversial definition of reverse remodelling following STEMI. Fourth, we did not analyse the use of medications or the effect of therapies in patients included as part of randomized trials. Fifth, we did not study the characteristics of the patients included in the CMR studies or analyse individual patient data. Sixth, the studies we included (both randomized controlled trials and cohort studies) demonstrated significant biases such as poor representativeness of all-comers STEMI patients, lack of blinding or small sample size. At last, CMR imaging was performed using the same scanner at baseline and at follow-up. However, it has been demonstrated that the effect of using different scanners did not affect significantly the data reproducibility, despite the variations in radio frequency coil architecture, sequences and software analysis used [57].

## Conclusions

LVR definition following STEMI using CMR imaging was highly variable among the studies, which included highly selected patients. Overall, the pooled LVR prevalence was 22.8%, 95% CI [19.4–26.7%]. The most frequent LVR criterion was a 20% increase in EDV or EDVI or a 15% increase in ESV or ESVI. According to the minimal detectable change for both EDV and ESV using CMR imaging in STEMI patients of 12%, a composite cut-off value of a 12 to 15% increase in ESV and a 12 to 20% increase in EDV using a follow-up CMR imaging 3 months after STEMI might be proposed as a consensual cut-off for defining adverse LVR for future CMR studies. There is a need for large-sized, prospective, adequately designed studies with serial CMR imaging and long-term follow-up in unselected patients in order to clarify the optimal LVR definition, the timing of its assessment, its impact on outcomes and strategies to prevent, stabilize or reverse its detrimental effects.

**Authors' contributions** Damien Legallois extracted and analysed the data and drafted the manuscript. Amir Hodzic extracted the data. Joachim Alexandre, Charles Dolladille, Alain Manrique, Vincent Roule and Paul Milliez participated in data analysis and revised the manuscript for important intellectual content. Eric Saloux and Fabien Labombarda revised the manuscript. Farzin Beygui designed the study, analysed the data and revised the manuscript for important intellectual content.

**Data availability** All data generated or analysed during this study are included in this published article and its supplementary information files ([Online Resource](#)).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

## References

1. Cohn JN, Ferrari R, Sharpe N (2000) Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an international forum on cardiac remodeling. *J Am Coll Cardiol* 35(3):569–582. [https://doi.org/10.1016/s0735-1097\(99\)00630-0](https://doi.org/10.1016/s0735-1097(99)00630-0)
2. Dorn GW 2nd (2009) Novel pharmacotherapies to abrogate postinfarction ventricular remodeling. *Nat Rev Cardiol* 6(4):283–291. <https://doi.org/10.1038/nrcardio.2009.12>
3. Bauters C, Dubois E, Porouchani S, Saloux E, Fertin M, de Groote P, Lamblin N, Pinet F (2017) Long-term prognostic impact of left ventricular remodeling after a first myocardial infarction in modern clinical practice. *PLoS One* 12:e0188884. <https://doi.org/10.1371/journal.pone.0188884>
4. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ (2000) Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2(4):271–278. <https://doi.org/10.3109/10976640009148691>
5. Bolognese L, Neskovic AN, Parodi G, Cerisano G, Buonamici P, Santoro GM, Antoniucci D (2002) Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications. *Circulation* 106(18):2351–2357. <https://doi.org/10.1161/01.cir.0000036014.90197.4a>
6. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group, Cochrane Statistical Methods Group (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. (2011) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Assessed 2020-04-04.
8. Fabregat-Andrés Ó, Ridocci-Soriano F, Estornell-Erill J, Corbí-Pascual M, Valle-Muñoz A, Berenguer-Jofresa A, Barrabés JA, Mata M, Monsalve M (2015) Blood PGC-1α concentration predicts myocardial salvage and ventricular remodeling after ST-segment elevation acute myocardial infarction. *Rev Esp Cardiol* 68(5):408–416. <https://doi.org/10.1016/j.rec.2014.05.020>
9. Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuvana AN, Treibel TA, Fontana M, Ramlall M, Hamarneh A, Sirker A, Herrey AS, Manisty C, Yellon DM, Kellman P, Moon JC, Hausenloy DJ (2016) Residual myocardial iron following intramyocardial hemorrhage during the convalescent phase of reperfused ST-segment-elevation myocardial infarction and adverse left ventricular remodeling. *Circ Cardiovasc Imaging* 9(10):e004940. <https://doi.org/10.1161/CIRCIMAGING.116.004940>
10. Mele D, Nardoza M, Chiodi E (2017) Early speckle-tracking echocardiography predicts left ventricle remodeling after acute ST-segment elevation myocardial infarction. *J Cardiovasc Echogr* 27(3):93–98. [https://doi.org/10.4103/jcecho.jcecho\\_2\\_17](https://doi.org/10.4103/jcecho.jcecho_2_17)
11. Biesbroek PS, Amier RP, Teunissen PFA, Hofman MBM, Robbers LFHJ, van de Ven PM, Beek AM, van Rossum AC, van Royen N, Nijveldt R (2017) Changes in remote myocardial tissue after acute myocardial infarction and its relation to cardiac remodeling: a CMR T1 mapping study. *PLoS One* 12(6):e0180115. <https://doi.org/10.1371/journal.pone.0180115>
12. O'Regan DP, Shi W, Ariff B, Baks AJ, Durighel G, Rueckert D, Cook SA (2012) Remodeling after acute myocardial infarction:

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Heart Fail Rev

- mapping ventricular dilatation using three dimensional CMR image registration. *J Cardiovasc Magn Reson* 14:41. <https://doi.org/10.1186/1532-429X-14-41>
13. Reinstadler SJ, Klug G, Feistritz HJ, Mayr A, Harrasser B, Mair J, Bader K, Streil K, Hammerer-Lercher A, Esterhammer R, Metzler B (2013) Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. *Heart* 99(20):1525–1529. <https://doi.org/10.1136/heartjnl-2013-303975>
  14. van Melle JP, van der Vleuten PA, Hummel YM, Nijveldt R, Tio RA, Voors AA, Zijlstra F (2010) Predictive value of tissue doppler imaging for left ventricular ejection fraction, remodeling, and infarct size after percutaneous coronary intervention for acute myocardial infarction. *Eur J Echocardiogr* 11(7):596–601. <https://doi.org/10.1093/ije/echocardiography/jeq023>
  15. Garg P, Broadbent DA, Swoboda PP, Foley JRJ, Fent GJ, Musa TA, Ripley DP, Erhayiem B, Dobson LE, McDiarmid AK, Haaf P, Kidambi A, Crandon S, Chew PG, van der Geest RJ, Greenwood JP, Plein S (2017) Extra-cellular expansion in the normal, non-infarcted myocardium is associated with worsening of regional myocardial function after acute myocardial infarction. *J Cardiovasc Magn Reson* 19(1):73. <https://doi.org/10.1186/s12968-017-0384-0>
  16. Shetye AM, Nazir SA, Razvi NA, Price N, Khan JN, Lai FY, Squire IB, McCann GP, Arnold JR (2017) Comparison of global myocardial strain assessed by cardiovascular magnetic resonance tagging and feature tracking to infarct size at predicting remodeling following STEMI. *BMC Cardiovasc Disord* 17(1):7. <https://doi.org/10.1186/s12872-016-0461-6>
  17. Pokorney SD, Rodriguez JF, Ortiz JT, Lee DC, Bonow RO, Wu E (2012) Infarct healing is a dynamic process following acute myocardial infarction. *J Cardiovasc Magn Reson* 14:62. <https://doi.org/10.1186/1532-429X-14-62>
  18. Sörensson P, Rydén L, Saleh N, Tomvall P, Arheden H, Pernow J (2013) Long-term impact of postconditioning on infarct size and left ventricular ejection fraction in patients with ST-elevation myocardial infarction. *BMC Cardiovasc Disord* 13:22. <https://doi.org/10.1186/1471-2261-13-22>
  19. Sugano A, Seo Y, Ishizu T, Watabe H, Yamamoto M, Machino-Ohtsuka T, Takaiwa Y, Kakefuda Y, Aihara H, Fumikura Y, Nishina H, Noguchi Y, Aonuma K (2017) Value of 3-dimensional speckle tracking echocardiography in the prediction of microvascular obstruction and left ventricular remodeling in patients with ST-elevation myocardial infarction. *Circ J* 81(3):353–360. <https://doi.org/10.1253/circj.CJ-16-0944>
  20. Gohbara M, Iwahashi N, Kataoka S, Hayakawa Y, Sakamaki K, Akiyama E, Maejima N, Tsukahara K, Hibi K, Kosuge M, Ebina T, Umemura S, Kimura K (2015) Glycemic variability determined by continuous glucose monitoring system predicts left ventricular remodeling in patients with a first ST-segment elevation myocardial infarction. *Circ J* 79(5):1092–1099. <https://doi.org/10.1253/circj.CJ-14-1226>
  21. Mangion K, Carrick D, Hennigan BW, Payne AR, McClure J, Mason M, Das R, Wilson R, Edwards RJ, Petrie MC, McEntegart M, Eteiba H, Oldroyd KG, Berry C (2016) Infarct size and left ventricular remodeling after preventive percutaneous coronary intervention. *Heart* 102(24):1980–1987. <https://doi.org/10.1136/heartjnl-2015-30866>
  22. Cha MJ, Lee JH, Jung HN, Kim Y, Choe YH, Kim SM (2019) Cardiac magnetic resonance-tissue tracking for the early prediction of adverse left ventricular remodeling after ST-segment elevation myocardial infarction. *Int J Card Imaging* 35(11):2095–2102. <https://doi.org/10.1007/s10554-019-01659-w>
  23. Yoon CH, Chung WY, Suh JW, Cho YS, Youn TJ, Chun EJ, Choi SI, Chae IH, Choi DJ (2013) Distal protection device aggravated microvascular obstruction evaluated by cardiac MR after primary percutaneous intervention for ST-elevation myocardial infarction. *Int J Cardiol* 167(5):2002–2007. <https://doi.org/10.1016/j.ijcard.2012.05.029>
  24. Watabe H, Sato A, Nishina H, Hoshi T, Sugano A, Kakefuda Y, Takaiwa Y, Aihara H, Fumikura Y, Noguchi Y, Aonuma K (2016) Enhancement patterns detected by multidetector computed tomography are associated with microvascular obstruction and left ventricular remodeling in patients with acute myocardial infarction. *Eur Heart J* 37(8):684–692. <https://doi.org/10.1093/eurheartj/ehv467>
  25. Reindl M, Feistritz HJ, Reinstadler SJ, Mueller L, Tiller C, Brenner C, Mayr A, Henninger B, Mair J, Klug G, Metzler B (2019) Thyroid-stimulating hormone and adverse left ventricular remodeling following ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 8(8):717–726. <https://doi.org/10.1177/2048872618770600>
  26. Tanimoto T, Imanishi T, Kitabata H, Nakamura N, Kimura K, Yamano T, Ishibashi K, Komukai K, Ino Y, Takarada S, Kubo T, Hirata K, Mizukoshi M, Tanaka A, Akasaka T (2010) Prevalence and clinical significance of papillary muscle infarction detected by late gadolinium-enhanced magnetic resonance imaging in patients with ST-segment elevation myocardial infarction. *Circulation* 122(22):2281–2287. <https://doi.org/10.1161/CIRCULATIONAHA.109.935338>
  27. Eitel I, Friedenberger J, Fuernau G, Dumjahn A, Desch S, Schuler G, Thiele H (2011) Intracoronary versus intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: 6-month effects on infarct size and left ventricular function. The randomised leipzig immediate percutaneous coronary intervention abciximab i.v. versus i.c. in ST-elevation myocardial infarction trial (LIPSIAbciximab-STEMI). *Clin Res Cardiol* 100(5):425–432. <https://doi.org/10.1007/s00392-010-0260-5>
  28. Huttin O, Mandry D, Eschaliere R, Zhang L, Micard E, Odille F, Beaumont M, Fay R, Felblinger J, Camenzind E, Zannad F, Gierd N, Marie PY (2017) Cardiac remodeling following reperfusion acute myocardial infarction is linked to the concomitant evolution of vascular function as assessed by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 19(1):2. <https://doi.org/10.1186/s12968-016-0314-6>
  29. Gerbaud E, Montaudon M, Chassieraud W, Gilbert S, Cochet H, Pucheu Y, Horovitz A, Bonnet J, Douard H, Coste P (2014) Effect of ivabradine on left ventricular remodeling after reperfusion myocardial infarction: a pilot study. *Arch Cardiovasc Dis* 107(1):33–41. <https://doi.org/10.1016/j.acvd.2013.12.001>
  30. García G, de la Chao Barca JM, Mirebeau-Prunier D, Reynier P, Furber A, Prunier F, Bière L (2019) Metabolomic approach in STEMI-patients undergoing left ventricular remodeling. *Int J Mol Sci* 20(2):E289. <https://doi.org/10.3390/ijms20020289>
  31. Caldentey G, García De Frutos P, Cristóbal H, Garabito M, Berrueto A, Bosch X, San Antonio R, Flores-Umanzor E, Perea RJ, De Caralt TM, Rodríguez J, Ortiz-Pérez JT (2017) Serum levels of growth arrest-specific 6 protein and soluble AXL in patients with ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 8(8):708–716. <https://doi.org/10.1177/2048872617740833>
  32. Huser O, Monmèneu JV, Sanchis J, Nunez J, Lopez-Lereu MP, Bonanad C, Chaustre F, Gomez C, Bosch MJ, Hinarejos R, Chorro FJ, Riegger GA, Llacer A, Bodi V (2013) Cardiovascular magnetic resonance-derived intramyocardial hemorrhage after STEMI: influence on long-term prognosis, adverse left ventricular remodeling and relationship with microvascular obstruction. *Int J Cardiol* 167(5):2047–2054. <https://doi.org/10.1016/j.ijcard.2012.05.05>
  33. Carberry J, Carrick D, Haig C, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay M, Davie A, Mahrous A, Ford I, Sattar N, Welsh P, Radjenovic A, Oldroyd KG, Berry C (2017) Persistence of infarct zone T2 hyperintensity at 6

- months after acute ST-segment-elevation myocardial infarction: incidence, pathophysiology, and prognostic implications. *Circ Cardiovasc Imaging* 10(12):e006586. <https://doi.org/10.1161/CIRCIMAGING.117.006586>
34. Rodriguez-Palmares JF, Gavara J, Ferreira-González I, Valente F, Rios C, Rodriguez-García J, Bonanad C, García Del Blanco B, Miñana G, Mutuberria M, Nuñez J, Barrabés J, Evangelista A, Bodí V, García-Dorado D (2019) Prognostic value of initial left ventricular remodeling in patients with reperused STEMI. *JACC Cardiovasc Imaging* 12(12):2445–2456. <https://doi.org/10.1016/j.jcmg.2019.02.025>
  35. Symons R, Masci PG, Francone M, Claus P, Barison A, Carbone I, Agati L, Galea N, Janssens S, Bogaert J (2016) Impact of active smoking on myocardial infarction severity in reperused ST-segment elevation myocardial infarction patients: the smoker's paradox revisited. *Eur Heart J* 37(36):2756–2764. <https://doi.org/10.1093/eurheartj/ehv738>
  36. Shetelig C, Limalanathan S, Hoffmann P, Seljeflot I, Gran JM, Eritsland J, Andersen GØ (2018) Association of IL-8 with infarct size and clinical outcomes in patients with STEMI. *J Am Coll Cardiol* 72(2):187–198. <https://doi.org/10.1016/j.jacc.2018.04.053>
  37. Wong DT, Leung MC, Das R, Liew GY, Teo KS, Chew DP, Meredith IT, Worthley MI, Worthley SG (2013) Intracoronary ECG during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction predicts microvascular obstruction and infarct size. *Int J Cardiol* 165(1):61–66. <https://doi.org/10.1016/j.ijcard.2011.07.078>
  38. Hallén J, Jensen JK, Fagerland MW, Jaffe AS, Atar D (2010) Cardiac troponin I for the prediction of functional recovery and left ventricular remodelling following primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Heart* 96(23):1892–1897. <https://doi.org/10.1016/10.1136/hrt.2009.190819>
  39. Janssens SP, Bogaert J, Zalewski J, Toth A, Adriaenssens T, Belmans A, Bennett J, Claus P, Desmet W, Dubois C, Goetschalckx K, Sinnaeve P, Vandenbergh K, Vermeersch P, Lux A, Szeli Z, Durak M, Lech P, Zmudka K, Pokreisz P, Vranckx P, Merkely B, Bloch KD, Van de Werf F, NOMI investigators (2018) Nitric oxide for inhalation in ST-elevation myocardial infarction (NOMI): a multicentre, double-blind, randomized controlled trial. *Eur Heart J* 39(29):2717–2725. <https://doi.org/10.1093/eurheartj/ehy232>
  40. Najjar SS, Rao SV, Melloni C, Raman SV, Povsic TJ, Melton L, Barsness GW, Prather K, Heitner JF, Kilaru R, Gruberg L, Hasselblad V, Greenbaum AB, Patel M, Kim RJ, Talan M, Ferrucci L, Longo DL, Lakatta EG, Harrington RA, Investigators REVEAL (2011) Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. *JAMA* 305(18):1863–1872. <https://doi.org/10.1001/jama.2011.592>
  41. Grabmaier U, Clauss S, Gross L, Klier I, Franz WM, Steinbeck G, Wakili R, Theiss HD, Brenner C (2017) Diagnostic and prognostic value of miR-1 and miR-29b on adverse ventricular remodeling after acute myocardial infarction - The SITAGRAMI-miR analysis. *Int J Cardiol* 244:30–36. <https://doi.org/10.1016/j.ijcard.2017.06.054>
  42. Achilli F, Malafonte C, Maggolini S, Lenatti L, Squadroni L, Gibelli G, Capogrossi MC, Dadone V, Gentile F, Bassetti B, Di Gennaro F, Camisasca P, Calchera I, Valagussa L, Colombo GI, Pompilio G, STEM-AMI trial Investigators (2014) G-CSF treatment for STEMI: final 3-year follow-up of the randomised placebo-controlled STEM-AMI trial. *Heart* 100(7):574–581. <https://doi.org/10.1136/heartjnl-2013-304955>
  43. Traverse JH, McKenna DH, Harvey K, Jorgensen BC, Olson RE, Bostrom N, Kadidlo D, Lesser JR, Jagadeesan V, Garberich R, Henry TD (2010) Results of a phase 1, randomized, double-blind, placebo-controlled trial of bone marrow mononuclear stem cell administration in patients following ST-elevation myocardial infarction. *Am Heart J* 160(3):428–434. <https://doi.org/10.1016/j.ahj.2010.06.009>
  44. Sünder D, Manka R, Moccetti T, Lo Cicero V, Emmert MY, Klersy C, Soncin S, Turchetto L, Radrianni M, Zuber M, Windecker S, Moschovitis A, Bühler I, Kozerke S, Erne P, Lüscher TF, Corti R (2016) Effect of bone marrow-derived mononuclear cell treatment, early or late after acute myocardial infarction: twelve months CMR and long-term clinical results. *Circ Res* 119(3):481–490. <https://doi.org/10.1161/CIRCRESAHA.116.308639>
  45. Granger CB, Bates ER, Jollis JG, Antman EM, Nichol G, O'Connor RE, Gregory T, Roettig ML, Peng SA, Ellrodt G, Henry TD, French WJ, Jacobs AK (2019) Improving care of STEMI in the United States 2008 to 2012. *J Am Heart Assoc* 8(1):e008096. <https://doi.org/10.1161/JAHA.118.008096>
  46. Belle L, Cayla G, Cottin Y, Coste P, Khalife K, Labèque JN, Farah B, Perret T, Goldstein P, Gueugniat PY, Braun F, Gauthier J, Gilard M, Le Heuzey JY, Naccache N, Drouet E, Bataille V, Ferrières J, Puymirat E, Schiele F, Simon T, Danchin N, FAST-MI 2015 investigators (2017) French registry on acute ST-elevation and non-ST-elevation myocardial infarction 2015 (FAST-MI 2015). Design and baseline data. *Arch Cardiovasc Dis* 110(6-7):366–378. <https://doi.org/10.1016/j.acvd.2017.05.001>
  47. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ (2002) Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 90(1):29–34. [https://doi.org/10.1016/s0002-9149\(02\)02381-0](https://doi.org/10.1016/s0002-9149(02)02381-0)
  48. Reindl M, Reinstadler SJ, Tiller C, Feistritz HJ, Kofler M, Brix A, Mayr A, Klug G, Metzler B (2019) Prognosis-based definition of left ventricular remodeling after ST-elevation myocardial infarction. *Eur Radiol* 29(5):2330–2339. <https://doi.org/10.1007/s00330-018-5875-3>
  49. Masci PG, Pavon AG, Pontone G, Symons R, Lorenzoni V, Francone M, Zalewski J, Barison A, Guglielmo M, Aquaro GD, Galea N, Muscogiuri G, Muller O, Carbone I, Baggiano A, Iglesias JF, Nessler J, Andreini D, Camici PG, Claus P, Luca L, Agati L, Janssens S, Schwitzer J, Bogaert J (2019) Early or deferred cardiovascular magnetic resonance after ST-segment-elevation myocardial infarction for effective risk stratification. *Eur Heart J Cardiovasc Imaging* jez179. <https://doi.org/10.1093/ehjci/jez179>
  50. Symons R, Pontone G, Schwitzer J, Francone M, Iglesias JF, Barison A, Zalewski J, de Luca L, Degrauwe S, Claus P, Guglielmo M, Nessler J, Carbone I, Ferro G, Durak M, Magistrelli P, Lo Presti A, Aquaro GD, Eeckhout E, Roguelov C, Andreini D, Vogt P, Guaricci AI, Mushtaq S, Lorenzoni V, Muller O, Desmet W, Agati L, Janssens S, Bogaert J, Masci PG (2018) Long-term incremental prognostic value of cardiovascular magnetic resonance after ST-segment elevation myocardial infarction: a study of the collaborative registry on CMR in STEMI. *JACC Cardiovasc Imaging* 11(6):813–825. <https://doi.org/10.1016/j.jcmg.2017.05.023>
  51. Hamirani YS, Wong A, Kramer CM, Salerno M (2014) Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 7(9):940–952. <https://doi.org/10.1016/j.jcmg.2014.06.012>
  52. Bulluck H, Dharmakumar R, Arai AE, Berry C, Hausenloy DJ (2018) Cardiovascular magnetic resonance in acute ST-segment-elevation myocardial infarction: recent advances, controversies, and future directions. *Circulation* 137(18):1949–1964. <https://doi.org/10.1161/CIRCULATIONAHA.117.03069>
  53. Klem I, Heiberg E, van Assche L, Parker MA, Kim HW, Grizzard JD, Arheden H, Kim RJ (2017) Sources of variability in quantification of cardiovascular magnetic resonance infarct size -

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- reproducibility among three core laboratories. *J Cardiovasc Magn Reson* 19(1):62. <https://doi.org/10.1186/s12968-017-0378-y>
54. Beygui F, Van Belle E, Ecollan P, Machecourt J, Hamm CW, Lopez De Sa E, Flather M, Verheugt FWA, Vicaut E, Zannad F, Pitt B, Montalescot G (2018) Individual participant data analysis of two trials on aldosterone blockade in myocardial infarction. *Heart* 104(22):1843–1849. <https://doi.org/10.1136/heartjnl-2018-312950>
55. Bulluck H, Go YY, Crimi G, Ludman AJ, Rosmini S, Abdel-Gadir A, Bhuva AN, Treibel TA, Fontana M, Pica S, Raineri C, Sirkar A, Herrey AS, Manisty C, Groves A, Moon JC, Hausenloy DJ (2017) Defining left ventricular remodeling following acute ST-segment elevation myocardial infarction using cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 19(1):26. <https://doi.org/10.1186/s12968-017-0343-9>
56. Mather AN, Fairbairn TA, Artis NJ, Greenwood JP, Plein S (2011) Timing of cardiovascular MR imaging after acute myocardial infarction: effect on estimates of infarct characteristics and prediction of late ventricular remodeling. *Radiology* 261(1):116–126. <https://doi.org/10.1148/radiol.11110228>
57. Gandy SJ, Waugh SA, Nicholas RS, Simpson HJ, Milne W, Houston JG (2008) Comparison of the reproducibility of quantitative cardiac left ventricular assessments in healthy volunteers using different MRI scanners: a multicenter simulation. *J Magn Reson Imaging* 28(2):359–365. <https://doi.org/10.1002/jmri.21401>

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## Étude REMOD-TEP

*Évaluation de la fonction endothéliale coronaire et de la fibrose myocardique en Tomographie par Émission de Positons (TEP) au décours d'un syndrome coronarien aigu avec sus-décalage du segment ST : relation avec le REMODElage ventriculaire gauche. Investigateur coordinateur : Dr Damien Legallois.*

### Rationnel

Le phénotype de RVG concerne l'ensemble du myocarde après un SCA (Figure 1). La zone "remote" joue un rôle dans ce RVG post-infarctus (données précliniques) et pourrait même être une cible thérapeutique potentielle [63]. Le rôle de la zone saine sur le RVG est mal connu chez l'homme et l'essentiel de la littérature sur le sujet est récent et postérieur à la date de début de ce travail de thèse [64–66].

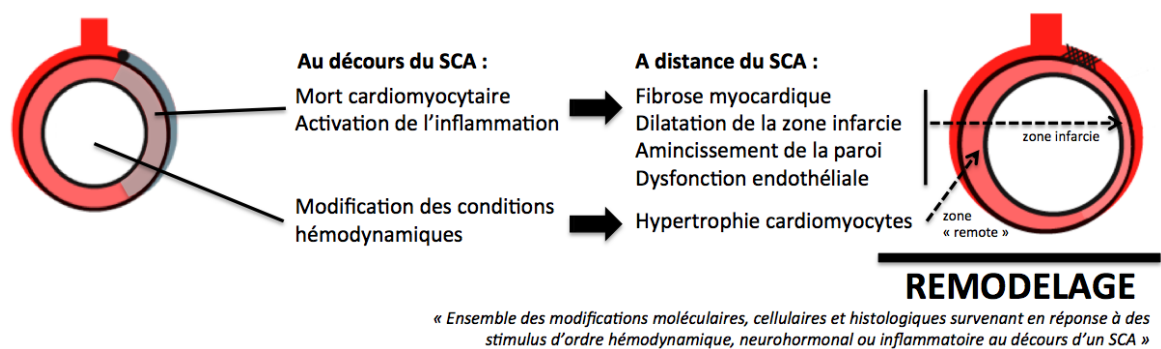


Fig. 1 Le remodelage ventriculaire gauche a pour conséquences une augmentation des volumes ventriculaires, une diminution de la fonction cardiaque et aboutit à l'apparition de signes fonctionnels et cliniques d'IC. La zone remote – controlatérale à l'occlusion coronaire – subit aussi des modifications tissulaires, et donc, un remodelage.

### **Présentation de l'étude**

REMOD-TEP est une étude prospective monocentrique, incluant une partie des patients du registre RESIST pour lesquels les données biologiques et d'imagerie sont plus exhaustives. L'objectif est d'inclure 30 patients pris en charge pour un premier STEMI, ayant une atteinte monotronculaire à la coronarographie et revascularisés à la phase aiguë. Ces patients ont une tomographie par émission de positons à l'eau marquée et test au froid à 3 mois de l'épisode, afin de quantifier dans la zone de l'infarctus et dans la zone remote non directement concernée par l'occlusion coronaire :

- la fonction endothéliale coronaire de façon non invasive. En effet, l'eau marquée est un traceur librement diffusible, permettant de quantifier précisément le débit coronaire local. L'utilisation conjointe d'un test au froid par application d'un coussin glacé sur les jambes permet d'induire une vasodilatation coronaire en cas de fonction endothéliale normale. En cas d'anomalie de la fonction endothéliale, la réponse est atténuée, voire inversée avec mise en évidence d'une vasoconstriction paradoxale.
- la fraction de tissu perfusable, reflet de la fibrose myocardique

### **Modalités de réalisation de l'examen TEP**

Les modalités de l'examen sont similaires à celles de notre précédente étude chez le patient ayant une cardiopathie dilatée non ischémique (Figure 2) [67]. Brièvement, les examens sont réalisés au GIP Cycéron, à Caen. La faible demi-vie de l'oxygène-15 (2,04 minutes) impose que la production d'oxygène-15 (par un cyclotron), la synthèse de l'eau marquée, son administration au patient et l'imagerie TEP se déroule en moins de 10 minutes.

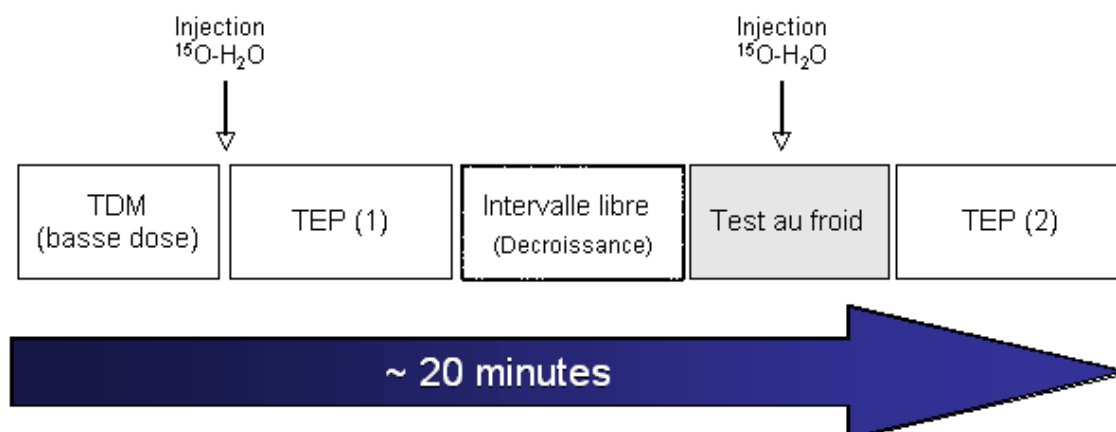


Fig. 2 **REMOT-TEP : modalités de réalisation de l'examen TEP.** TEP, Tomographie par Émission de Positons ; TDM, tomodensitométrie.

### Financement du projet

Le budget a été évalué à 58660 euros. Cette étude a été financée (i) par l'appel à projet Emergence du GIRCI Nord-Ouest (octobre 2015) à hauteur de 40000 euros et, (ii) par la bourse "Les syndromes coronariens aigus" de la Société Française de Cardiologie (décembre 2015), pour un montant de 20000 euros.

### Réglementaire

- Autorisation d'essai clinique par l'Agence Nationale de Sécurité du Médicament et des produits de santé, le 01 décembre 2015
- Comité de Protection des Personnes Nord-Ouest III, le 09 janvier 2016
- Autorisation de lancement d'étude (CHU de Caen), le 01 mars 2016
- Enregistrement clinicaltrials.gov : NCT02789098
- Début des inclusions le 25 mai 2016

### **Déroulement de l'étude**

La première inclusion a eu lieu le 13 octobre 2016. Le rythme des inclusions a ensuite pu continuer selon le rythme prédéfini. Ainsi, en mai 2017, dix patients – soit un tiers de l'effectif total initial attendu – avaient été inclus.

Malheureusement, une panne va conduire à l'arrêt de la production d'eau marquée durant le printemps 2017. Cette activité est toujours suspendue pour l'heure. Seuls les 4 premiers patients inclus ont pu terminer le protocole avec réalisation de l'examen TEP à 3 mois du SCA. Les 6 autres patients inclus n'ont pu avoir leur examen car la panne est survenue entre leur inclusion et l'imagerie prévue à 3 mois.

## **Relation entre le strain atrial gauche et le remodelage ventriculaire gauche**

Dans le contexte de SCA, la dilatation de l'oreillette gauche (OG) est associée à une augmentation des pressions de remplissage ventriculaire gauche (PRVG) et est un marqueur de mauvais pronostic (mortalité ou hospitalisation pour IC) [68, 69]. Cette étude vise à étudier le lien entre les paramètres de fonction atriale gauche et le RVG chez les patients de la cohorte RESIST pour lesquels nous disposons d'échocardiographie à la phase initiale du STEMI et au cours du suivi.

La méthode utilisée est celle de la mesure du strain de l'OG par speckle tracking [70]. Brièvement, cette technique consiste à suivre la déformation locale du myocarde en analysant le déplacement de marqueurs acoustiques naturels au sein de la paroi myocardique. Il est commun d'étudier 3 composantes au strain de l'OG (Figure 3). Tout d'abord la fonction réservoir, dépendante de la relaxation et de la compliance atriale et de la descente du plancher basal du VG durant la systole ventriculaire. Celle-ci est calculée en mesurant la différence des valeurs de strain entre la fin de la diastole et la réouverture mitrale (et comprend donc les phases de contraction isovolumique, d'éjection ventriculaire et de relaxation isovolumique). La fonction conduit est mesurée entre l'ouverture de la valve mitrale et le début de la contraction de l'OG et est dépendante de la fonction diastolique du VG et notamment de la succion exercée par ce dernier au moment de sa détorsion, en début de diastole. La dernière composante est la composante contractile, fonction de la contractilité atriale gauche, de la compliance du VG et des PRVG. Elle se mesure entre le début de la contraction atriale et la fermeture de la valve mitrale, en fin de diastole.

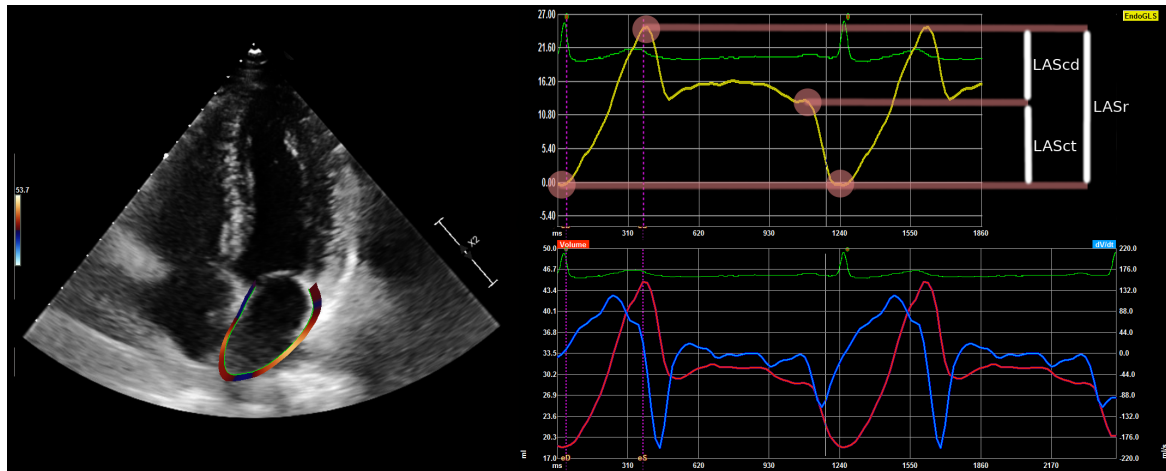


Fig. 3 **Mesure du strain de l'oreillette gauche en échocardiographie.** Il est possible d'individualiser la fonction réservoir (LASr), mesurée entre la fin de la diastole et l'ouverture de la valve mitrale, la fonction conduit (LAScd) entre l'ouverture de la valve mitrale et le début de la contraction de l'OG et la fonction contractile (LASct), entre le début de la contraction atriale et la fermeture de valve mitrale.

Nous avons ainsi mesuré les fonctions réservoir, conduit et pompe de l'OG à la phase aiguë du STEMI et avons étudié leurs relations avec le RVG au cours du suivi à 6 mois dans une population de 121 patients. Les données échocardiographiques ont été traitées suivant les recommandations et documents de consensus [71, 72], notamment en ce qui concerne l'évaluation du strain de l'OG [73].

La comparaison des patients ayant présenté un RVG (défini comme une augmentation d'au moins 20% du volume télédiastolique, mesuré en échocardiographie 3D) avec ceux n'ayant pas présenté de remodelage montre une meilleure fonction pompe dans ce dernier groupe. Cette association persiste après ajustement sur les volumes ventriculaires initiaux. En revanche, il n'y a pas de corrélation entre les valeurs des composantes de strain réservoir ou conduit et l'évolution des volumes ventriculaires gauches au cours du suivi.

**Legallois D**, Hodzic A, Milliez P, Manrique A, Saloux E, Beygui F.

Left atrial strain quantified after myocardial infarction is associated with ventricular remodeling.

Soumis à American Journal of Cardiology.

Le poster accepté à l'ESC 2020 est reproduit, page 190.

## **Left atrial strain quantified after myocardial infarction is associated with ventricular remodeling**

**Short title:** Atrial strain and remodeling after AMI

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Total word count: 3036 words

**ABSTRACT**

**Background.** Left ventricular remodeling (LVR) is common and associated with adverse outcome after ST-elevation myocardial infarction (STEMI). We aimed to investigate the association between left atrial (LA) mechanical function using speckle tracking imaging and LVR at follow-up in STEMI patients.

**Methods.** Baseline 3D thoracic echocardiograms were performed within 48 hours following admission and 6 months after STEMI. A >20% increase in the left ventricular end-diastolic volume compared to baseline at 6 months of follow-up was defined as LVR. LA global longitudinal strain was evaluated for the reservoir, conduit, and contraction (LASct) phases.

**Results.** A total of 121 patients without clinical heart failure were prospectively included (age  $58.3 \pm 12.5$  years, male 98 (81%)). Baseline and follow-up left ventricular ejection fraction (LVEF) were 46.8% [41.0, 52.9] and 52.1% [45.8, 57.0] respectively ( $p < 0.001$ ). Compared to other patients, those with LVR had significantly lower values of LASct at baseline (-7.4% [-10.1, -6.5] vs. -9.9% [-12.8, -8.1],  $p < 0.01$ ), both on univariate and baseline LV volumes-adjusted analyses. Baseline LA strain for reservoir and conduit phases were not associated with significant LVR at follow-up.

**Conclusions.** Baseline LASct may help identifying patients without heart failure early after STEMI who are at higher risk of further LVR and subsequent heart failure and who may benefit from more intensive management.

**KEYWORDS:** ST-elevation myocardial infarction, left ventricular remodeling, left atrial strain

## INTRODUCTION

Despite major advances in coronary revascularization for ST-elevation myocardial infarction (STEMI), left ventricular remodeling (LVR) associated with mortality and heart failure (HF) remains common (1). LVR is the consequence of cellular and histological modifications (2), that are induced by deleterious adaptive mechanism involving the infarcted tissue and remote myocardium (3).

Larger left atrial (LA) volume is associated with chronic increased left ventricular (LV) filling pressure and has been described as a predictor of mortality and hospitalization for HF in patients with acute myocardial infarction (AMI) (4,5). However, there are controversial data about the correlation between LA volume and LVR (6,7). Therefore, the assessment of LA mechanical function may have additional prognostic value when compared to conventional echocardiographic measurements (8,9). Direct evaluation of atrial myocardial function using speckle-tracking imaging allows the assessment of active myocardial deformation as a marker of LA function (10,11).

The objective of our study was to investigate the association between LA mechanical function assessed early after STEMI and LVR at follow-up.

## MATERIALS AND METHODS

### Patient selection and data collection

This study was a prospective, observational study that included consecutive patients admitted for STEMI and successfully treated with either primary percutaneous coronary intervention (pPCI) or fibrinolysis followed by PCI, from June 2015 to October 2018.

Inclusion criteria were: age  $\geq 18$  years, ischaemic symptoms  $< 12$  hours, ECG with ST-segment elevation. Criteria for exclusion were unsuccessful revascularization (residual stenosis  $> 30\%$  in the culprit lesion and/or thrombolysis in myocardial infarction flow  $< 3$ ), clinical signs of HF as defined by Killip class  $\geq II$ , atrial fibrillation or non-cardiac-related conditions with estimated life expectancy

<12 months and follow-up planned in another center. Informed consent was obtained from all patients. Patients were not involved in setting the research question as echocardiography after STEMI is part of routine clinical practice. The study complied with the Declaration of Helsinki and was approved by the local ethics committee.

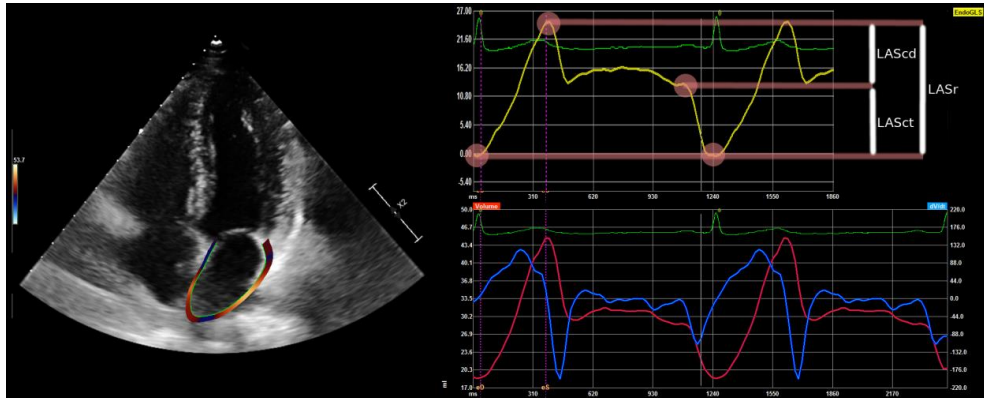
### **Echocardiography**

All subjects had 3D transthoracic echocardiogram within 48 hours after admission and at 6 months, using an EPIQ 7G (Phillips Healthcare, Best, Netherlands) equipped with a 1 to 5-MHz transthoracic matrix array transducer (XMATRIX X5-1). Two-dimensional grayscale harmonic images were acquired in the apical plane and in the short axis plane at a frame rate above 50 frames/sec. A 3D full volume was acquired from the apical view with minimum depth to optimize the frame rate. LV end-diastolic (EDV) and end-systolic volumes (ESV) were measured from the resulting three-dimensional volumes and were normalized by body surface area. Color Doppler and tissue Doppler acquisitions were acquired in concordance with the current ASE recommendations (12). Analysis of echocardiographic images was performed offline by two independent observers using dedicated softwares (Intellispace Cardiovascular software [Philips Healthcare, Best, Netherlands] and TomTec software [TomTec Imaging Systems GmbH, Unterschlessheim, Germany]). Diastolic function was assessed as stated in the current ASE/EACVI guidelines (13). LVR at follow-up was defined as a >20% increase in the EDV compared to baseline (14). Depending on the presence or absence of LVR at follow-up, patients were divided into two groups: LV remodeling (LVR+) and no LV remodeling (LVR-).

### **Analysis of LA volume and function**

LA volume was calculated according to the biplane Simpson method. Left atrial emptying fraction (LAEF) was calculated as:  $(\text{LA volume max} - \text{LA volume min}) / \text{LA volume max} \times 100$  (%). LA

myocardial deformation imaging was assessed following recently published consensus document (10). LA strain was measured using a non-foreshortened apical four chamber view of the left atrium (15), recorded with a frame rate of >40 fps. The user placed two points on the mitral annulus and a third point in the endocardium of the roof of the LA. The software automatically delineated the endocardial contour but could be manually adjusted by the user. The patient was retrospectively excluded if tracking was of poor quality. LA global longitudinal strain was reported separately for the reservoir (inflow during ventricular systole), conduit (passive emptying during ventricular relaxation and diastasis), and contraction phase (active emptying): (i) strain during reservoir phase (LASr) was measured by the difference of strain values at mitral valve opening and at ventricular end-diastole, (ii) strain during conduit phase (LAScd) was measured by the difference of strain values at the onset of atrial contraction and at mitral valve opening, and (iii) strain during contraction phase (LASct) was measured as the difference of strain values at ventricular end-diastole and at the onset of atrial contraction (Figure 1) (10). The time reference to define the zero-baseline for LA strain curves was set to ventricular end-diastole.



**Figure 1.** Left atrial strain assessment. Zero strain reference is set at end-diastole. Strain during reservoir phase (LASr) is calculated as the difference between onset of filling and end-diastole, strain during conduit phase (LAScd) is calculated as the difference between onset of atrial contraction and onset of filling and strain during contraction phase (LASct) is calculated as the difference between end-diastole and onset of atrial filling.

### Statistical analysis

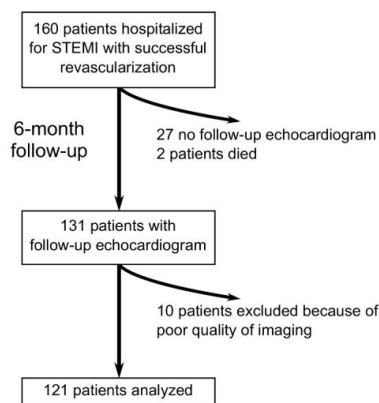
Continuous data are presented as mean $\pm$ SD or median [IQR] and categorical data are presented as frequencies and percentages. Differences in characteristics between patient groups were evaluated using the paired Student or Wilcoxon rank sum and  $\chi^2$  tests. Un-adjusted and, adjusted on baseline EDV or ESV linear and logistic regression models were carried out to assess the relationship between relative differences in LV volumes as a continuous variable and LVR as a binary variable and, baseline echocardiographic parameters. All statistical analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were 2-sided and used a significance threshold of  $p < 0.05$ .

## RESULTS

### Study population

Among the 160 patients with complete echocardiogram at baseline, 2 patients died during follow-up and 27 did not attend follow-up echocardiogram (Figure 2). Ten patients were retrospectively

excluded because of poor quality of imaging. Baseline characteristics of the remaining 121 patients are depicted in Table 1. Mean age was  $58.3 \pm 12.5$  years and 98 (81%) were men. The median time between symptom onset to revascularization was 3.8 hours [2.7, 5.2].



**Figure 2.** Flow chart.

#### Left ventricular volumes, function and filling

Baseline left ventricular ejection fraction (LVEF) was 46.8% [41.0, 52.9] and significantly improved to 52.1% [45.8, 57.0] at follow-up, ( $p < 0.001$ , Table 1). At follow-up, there was a significant increase of EDV index (from  $56.5 \text{ mL/m}^2$  [47.7, 66.4] to  $59.1 \text{ mL/m}^2$  [49.3, 72.4],  $p < 0.01$ ) without significant change in ESV index (from  $30.3 \text{ mL/m}^2$  [24.1, 36.1] to  $27.5 \text{ mL/m}^2$  [20.7, 39.8],  $p = 0.92$ ). Median deceleration time of the early mitral inflow was 200 ms [170, 235], E/A ratio was 0.96 [0.84, 1.20] and median E/e' ratio was 8.1 [7.1, 9.9]. Thirty-four patients had LVR at follow-up (28.1%). At follow-up, the improvement of LVEF in patients without LVR (54.0% [48.1, 59.4] vs. 48.2% [41.7, 53.5],  $p < 0.001$ ) was driven by a decrease in ESV ( $24.2 \text{ mL/m}^2$  [19.7, 30.9] vs.  $28.8 \text{ mL/m}^2$  [24.4, 36.2],  $p < 0.001$ ) without significant change regarding EDV (Table 1). Conversely, both EDV and ESV increased significantly in the LVR+ group ( $81.4 \text{ mL/m}^2$  [65.3, 92.4] vs.  $54.5 \text{ mL/m}^2$  [46.6, 62.9],

$p < 0.001$  and  $42.8 \text{ mL/m}^2$  [32.8, 52.9] vs.  $31.4 \text{ mL/m}^2$  [24.2, 35.8],  $p < 0.001$ ) without change regarding LVEF.

#### **Relationship between LVR and Left atrial strain volume and function**

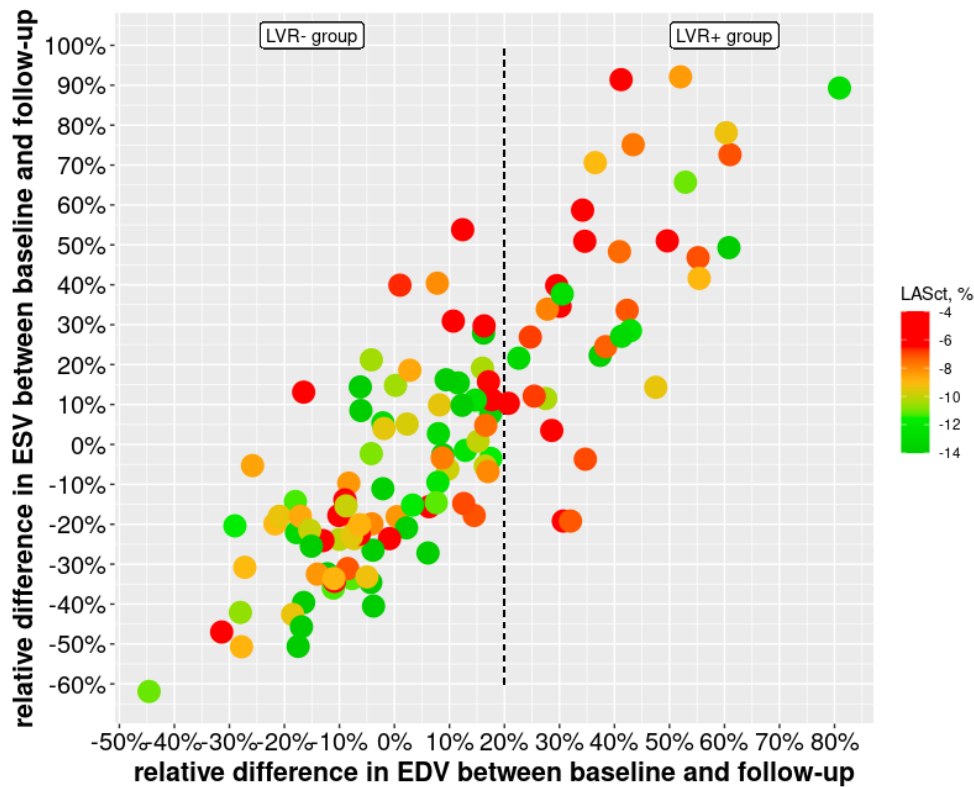
At baseline, only LASct was significantly different between groups ( $-7.4\%$  [-10.1, -6.5] in the LVR+ group vs.  $-9.9\%$  [-12.8, -8.1] in patients without LVR at follow-up ( $p < 0.01$ , Table 1), demonstrating a better LA pump function at baseline in the latter population. The relationship between the changes in LV volumes and LA pump function is depicted in Figure 3. No other differences were found between groups with respect to baseline LA volume and function, including LASr and LAScd ( $21.5\%$  [17.0, 24.7] vs.  $21.0\%$  [16.8, 26.1],  $p = 0.94$  and  $-12.6\%$  [-15.0, -9.5] vs.  $-11.4\%$  [-14.5, -8.3],  $p = 0.16$ , in the LVR+ and LVR- groups, respectively). Adjusted analyses on baseline EDV, ESV and LVEF showed that LASct was associated with LVR independent of baseline LV volumes (Table 2). Sensitivity analysis demonstrated same results (data not shown).

|                                              | Overall<br>(n=121)  | LVR+<br>(n=34)      | LVR-<br>(n=87)      | p<br>value |
|----------------------------------------------|---------------------|---------------------|---------------------|------------|
| Age, years                                   | 58.3±12.5           | 57.8±12.9           | 58.6±12.5           | 0.76       |
| Gender, male                                 | 98 (81.0%)          | 30 (88.2%)          | 68 (78.2%)          | 0.32       |
| Hypertension                                 | 43 (35.5%)          | 9 (26.5%)           | 34 (39.1%)          | 0.28       |
| Diabetes mellitus                            | 18 (14.9%)          | 5 (14.7%)           | 13 (14.9%)          | 1          |
| Hypercholesterolemia                         | 51 (42.1%)          | 16 (47.1%)          | 35 (40.2%)          | 0.64       |
| Current smoking                              | 82 (67.8%)          | 23 (67.6%)          | 59 (67.8%)          | 1          |
| Body Mass Index (kg/m <sup>2</sup> )         | 26.0 [24.2, 28.8]   | 26.0 [24.6, 27.2]   | 25.9 [23.8, 29.1]   | 0.76       |
| Symptoms-to-balloon time, hours              | 3.8 [2.7, 5.2]      | 3.9 [3.3, 6.1]      | 3.8 [2.6, 5.2]      | 0.46       |
| Echocardiography at baseline                 |                     |                     |                     |            |
| EDV, mL/m <sup>2</sup>                       | 56.5 [47.7, 66.4]   | 54.5 [46.6, 62.9]   | 58.0 [48.2, 67.6]   | 0.32       |
| ESV, mL/m <sup>2</sup>                       | 30.3 [24.1, 36.1]   | 31.4 [24.2, 35.8]   | 28.8 [24.4, 36.2]   | 0.89       |
| LVEF, %                                      | 46.8 [41.0, 52.9]   | 44.5 [39.1, 50.9]   | 48.2 [41.7, 53.5]   | 0.10       |
| E/A ratio                                    | 0.96 [0.84, 1.20]   | 1.00 [0.89, 1.18]   | 0.96 [0.78, 1.19]   | 0.27       |
| Deceleration time of early mitral inflow, ms | 200 [170, 235]      | 180 [163, 214]      | 200 [170, 240]      | 0.08       |
| Mean E/e' ratio                              | 8.1 [7.1, 9.9]      | 8.4 [7.0, 10.8]     | 8.0 [7.1, 9.6]      | 0.54       |
| Left atrial volume, mL/m <sup>2</sup>        | 32.1 [26.5, 38.9]   | 32.9 [27.6, 39.6]   | 32.0 [26.2, 38.5]   | 0.51       |
| LAEF, %                                      | 51.7±10.0           | 51.2±9.9            | 51.9±10.1           | 0.75       |
| LASr, %                                      | 21.4 [16.8, 25.8]   | 21.5 [17.0, 24.7]   | 21.0 [16.8, 26.1]   | 0.94       |
| LAScd, %                                     | -12.0 [-14.5, -8.8] | -12.6 [-15.0, -9.5] | -11.4 [-14.5, -8.3] | 0.16       |
| LASct, %                                     | -9.4 [-12.3, -7.1]  | -7.4 [-10.1, -6.5]  | -9.9 [-12.8, -8.1]  | <0.01      |
| Echocardiography at follow-up                |                     |                     |                     |            |
| EDV, mL/m <sup>2</sup>                       | 59.1 [49.3, 72.4]†  | 81.4 [65.3, 92.4]‡  | 54.2 [47.0, 67.1]   | <0.001     |
| ESV, mL/m <sup>2</sup>                       | 27.5 [20.7, 39.8]   | 42.8 [32.8, 52.9]‡  | 24.2 [19.7, 30.9]‡  | <0.001     |
| LVEF, %                                      | 52.1 [45.8, 57.0]‡  | 47.2 [39.3, 53.6]   | 54.0 [48.1, 59.4]‡  | 0.001      |

**Table 1.** Baseline characteristics and echocardiographic data according to LVR status. A: peak velocity of atrial diastolic filling, E: peak velocity of early diastolic filling, e': early mitral annular velocity, EDV: end-diastolic volume, ESV: end-systolic volume, LAEF: LA emptying fraction, LAScd: strain during conduit phase, LASct: strain during contraction phase, LASr: strain during reservoir phase, LVEF: LV ejection fraction, and STEMI: ST-elevation myocardial infarction. †p<0.01 and ‡p<0.001 vs. baseline.

|               | EDV-adjusted model |                     |                      |                  | ESV-adjusted model   |                  | EF-adjusted model    |                  |
|---------------|--------------------|---------------------|----------------------|------------------|----------------------|------------------|----------------------|------------------|
|               | OR, [95%CI]        | Un-adjusted p.value | Adjusted OR, [95%CI] | Adjusted p.value | Adjusted OR, [95%CI] | Adjusted p.value | Adjusted OR, [95%CI] | Adjusted p.value |
| DT, per 10 ms | 0.92 [0.85, 1.00]  | 0.0495              | 0.92 [0.85, 1.00]    | 0.07             | 0.92 [0.85, 1.00]    | 0.049            | 0.93 [0.86, 1.01]    | 0.07             |
| LASr, %       | 0.99 [0.94, 1.04]  | 0.63                | 0.98 [0.93, 1.04]    | 0.58             | 0.99 [0.93, 1.04]    | 0.63             | 1.00 [0.94, 1.06]    | 0.99             |
| LAScd, %      | 0.96 [0.90, 1.03]  | 0.23                | 0.96 [0.90, 1.03]    | 0.26             | 0.96 [0.90, 1.02]    | 0.22             | 0.94 [0.88, 1.01]    | 0.22             |
| LASct, %      | 1.19 [1.05, 1.34]  | <0.01               | 1.19 [1.05, 1.34]    | <0.01            | 1.19 [1.05, 1.34]    | <0.01            | 1.17 [1.04, 1.33]    | 0.02             |

**Table 2.** Association between LA parameters at baseline and LVR at follow-up. Univariate and bivariate analysis (adjusted for baseline LV volumes). DT: deceleration time of early mitral inflow, EDV: end-diastolic volume, EF: ejection fraction, ESV: end-systolic volume, LAScd: strain during conduit phase, LASct: strain during contraction phase, LASr: strain during reservoir phase.



**Figure 3.** Relationship between left atrial strain during contraction phase (LASct) and LVR, defined as a >20% increase in the EDV compared to baseline. EDV: end-diastolic volume, ESV: end-systolic volume. LASct is expressed as %.

## DISCUSSION

This study shows that baseline LA mechanical function using LASct assessment is independently associated with LVR at follow-up in STEMI patients. Close physiological interactions link LA and LV functions during cardiac cycle. The LA is a blood reservoir during LV systole. This function depends on both LA relaxation and compliance (16) and, LV systolic function through the descent of the LV base (17,18). During early diastole, LA and LV are directly connected and coupled. LAScd is reliant on LV diastolic function, including both the suction force dependent on LV relaxation and LV chamber stiffness (19,20). LA also acts as an active pump during late LV diastole. The latter LA booster function (LASct) is based on intrinsic LA contractility, LV compliance and LV end-diastolic pressure (LVEDP), as LA preload reserve decreases when LV filling pressures increase (11).

Altered LA function has been described in AMI (16,21). The aforementioned interactions between LA and LV are more complex after AMI where a preserved LASr can withstand the impact of the increased LA pressure due to LV dysfunction and maintain an adequate LV filling (22). A low LASr leads to impaired LV diastolic filling and reduced LV stroke volume (23,24). Both LA reservoir dysfunction and elevated LVEDP contribute to LA enlargement especially when combined. LA pump function contributes to up to 30% of total LV stroke volume in normal individuals and its contribution to LV filling and stroke volume is higher in patients with AMI (25). As reduced LVEF has been described as an independent determinant of impaired LA pump function (26), post-STEMI altered LVEF may lead to reduced LASct. LA passive ejection is altered in patients with AMI, which may be compensated by an increase in active contractile function of the LA (27). As a result, LV stroke volume can be maintained despite LV dysfunction (28). However, such conditions are associated with LA pressure overload, leading to both LA enlargement and dysfunction.

This study demonstrated that baseline LASct is associated with the changes of LV volumes at follow-up in a STEMI population with successful reperfusion and without clinical signs of HF. Few studies have assessed the relationship between LA function and the change of LV volumes and function after STEMI. A prior study assessing LA and LV functions within 48 hours and 12 months after admission

for AMI (22) showed that ESV and EDV decreased significantly, resulting in an increase in LVEF, regardless of the existence of LA remodeling. However, the relationship between LA strain at baseline and the changes of LV volumes and function during follow-up were not described. In our study, the association between low values of LASct and LVR may be a consequence of the aforementioned interactions between LV and LA. Reduced LASct may be an early sub-clinical and sub-anatomic marker of more extensive myocardial damage leading to reduced LV compliance and increased LVEDP. Such conditions as well as the subsequent modified interactions between LA booster function and LV function (29) may initiate the deleterious adaptive mechanical and neurohormonal responses (30) which ultimately leads to LVR. It has been described that reduced LVEF is an independent determinant of impaired LA pump function (26). As a consequence, it could be hypothesized that LV systolic dysfunction and LA pump function impairment may worsen each other in the setting of AMI. However, the present study argued that LA impairment may be the primary driver as we showed that (i) LASct was associated to LVR, independently of baseline LV volumes and, (ii) LA mechanical function impairment precedes LVR.

The present study has several limitations. The population is highly selected including only patients with successful myocardial reperfusion and revascularization, without HF and who had complete 3D-trans thoracic echocardiogram at 2 timepoints. The measurement of LA strain is software dependent and our results may not be generalized to other softwares. Finally, as in all cohort studies the cause-effect relationship may only be speculative and the impact of known or unknown covariables not analyzed in the present study on the LV remodeling remains unassessed.

## CONCLUSIONS

Our study showed that after STEMI, in patients with successful myocardial reperfusion and no clinical sign of HF, the contractile component of baseline LA strain was significantly associated with dynamic increase of EDV, indicating LVR. These findings suggest that there is a relationship between

LA function, LV function and adverse LVR after STEMI. Low values of LASct at baseline may be a sensitive sub-clinical and sub-anatomic marker of the extent of LV damage, helpful for identifying a subgroup of patients at higher risk of further LVR and HF.

#### **Competing Interests statement**

D. Legallois reports grant from Pfizer and personal fees from Astrazeneca, outside the submitted work. F. Beygui reports grants and non-financial support from Medtronic, grants and non-financial support from Biosensor, personal fees and non-financial support from BMS, outside the submitted work. There is no other competing interest to declare.

#### **Contributorship Statement**

D. Legallois: Data curation, Formal analysis, Writing - original draft;

A. Hodzic: Investigation, Writing - review & editing

P. Milliez: Supervision, Writing - review & editing

A. Manrique: Writing - review & editing

E. Saloux: Investigation, Software, Writing - review & editing

F. Beygui: Conceptualization, Methodology, Supervision, Writing - review & editing and Validation

## REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019; 40: 87-165.
2. Dorn GW 2nd. Novel pharmacotherapies to abrogate postinfarction ventricular remodeling. *Nat Rev Cardiol* 2009; 6: 283-91.
3. Symons R, Masci PG, Goetschalckx K, Doulatpis K, Janssens S, Bogaert J. Effect of infarct severity on regional and global left ventricular remodeling in patients with successfully reperfused ST segment elevation myocardial infarction. *Radiology*. 2015; 274: 93-102.
4. Meris A, Amigoni M, Uno H, Thune JJ, Verma A, Køber L, et al. Left atrial remodelling in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo study. *Eur Heart J* 2009; 30: 56-65.
5. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation* 2003; 107: 2207-12.
6. Joyce E, Hoogslag GE, Leong DP, Debonnaire P, Katsanos S, Boden H, et al. Association between left ventricular global longitudinal strain and adverse left ventricular dilatation after ST-segment-elevation myocardial infarction. *Circ Cardiovasc Imaging* 2014; 7: 74-81.
7. Na HM, Cho GY, Lee JM, Cha MJ, Yoon YE, Lee SP, et al. Echocardiographic Predictors for Left Ventricular Remodeling after Acute ST Elevation Myocardial Infarction with Low Risk Group: Speckle Tracking Analysis. *J Cardiovasc Ultrasound* 2016; 24: 128-134.
8. Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. *Cardiovasc Ultrasound* 2009; 7: 6.

9. Saraiva RM, Demirkol S, Buakhamsri A, Greenberg N, Popović ZB, Thomas JD, et al. Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. *J Am Soc Echocardiogr* 2010; 23: 172-80.
10. Badano LP, Kolas TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2018; 19: 591-600.
11. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; 73: 1961-77.
12. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-63.
13. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016; 29: 277-314.
14. Savoye C, Equine O, Tricot O, Nogue O, Segrestin B, Sautière K, Elkohen M, Pretorian EM, Taghipour K, Philias A, Aumégeat V, Decoulx E, Ennezat PV, Bauters C; REmodelage VEntriculaire study group. Left ventricular remodeling after anterior wall acute myocardial

- infarction in modern clinical practice (from the REmodelage VEntriculaire [REVE] study group). *Am J Cardiol*. 2006; 98: 1144-9.
15. Sutherland GR, Di Salvo G, Claus P, D'hooge J, Bijmens B. Strain and strain rate imaging: a new clinical approach to quantifying regional myocardial function. *J Am Soc Echocardiogr* 2004; 17: 788-802.
  16. Dogan C, Ozdemir N, Hatipoglu S, Bakal RB, Omaygenc MO, Dindar B, et al. Relation of left atrial peak systolic strain with left ventricular diastolic dysfunction and brain natriuretic peptide level in patients presenting with ST-elevation myocardial infarction. *Cardiovasc Ultrasound* 2013; 11: 24.
  17. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation* 1999; 100: 427-36.
  18. Hoit BD, Shao Y, Gabel M, Walsh RA. In vivo assessment of left atrial contractile performance in normal and pathological conditions using a time-varying elastance model. *Circulation* 1994; 89: 1829-38.
  19. Manning WJ, Silverman DI, Katz SE, Douglas PS. Atrial ejection force: a noninvasive assessment of atrial systolic function. *J Am Coll Cardiol* 1993; 22: 221-5.
  20. Toma Y, Matsuda Y, Moritani K, Ogawa H, Matsuzaki M, Kusukawa R. Left atrial filling in normal human subjects: relation between left atrial contraction and left atrial early filling. *Cardiovasc Res* 1987; 21: 255-9.
  21. Ersbøll M, Andersen MJ, Valeur N, Mogensen UM, Waziri H, Møller JE, et al. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. *Circ Cardiovasc Imaging* 2013; 6: 26-33.

22. Antoni ML, Ten Brinke EA, Marsan NA, Atary JZ, Holman ER, van der Wall EE, et al. Comprehensive assessment of changes in left atrial volumes and function after ST-segment elevation acute myocardial infarction: role of two-dimensional speckle-tracking strain imaging. *J Am Soc Echocardiogr* 2011; 24: 1126-33.
23. Eshoo S, Boyd AC, Ross DL, Marwick TH, Thomas L. Strain rate evaluation of phasic atrial function in hypertension. *Heart* 2009; 95: 1184-91.
24. Boyd AC, Ng AC, Tran da T, Chia EM, French JK, Leung DY, et al. Left atrial enlargement and phasic function in patients following non-ST elevation myocardial infarction. *J Am Soc Echocardiogr* 2010; 23: 1251-8.
25. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J* 2008; 156: 1056-64.
26. Kühl JT, Kofoed KF, Møller JE, Hammer-Hansen S, Kristensen T, Køber L, et al. Assessment of left atrial volume and mechanical function in ischemic heart disease: a multi slice computed tomography study. *Int J Cardiol* 2010; 145: 197-202.
27. Antoni ML, ten Brinke EA, Atary JZ, Marsan NA, Holman ER, Schalij MJ, et al. Left atrial strain is related to adverse events in patients after acute myocardial infarction treated with primary percutaneous coronary intervention. *Heart* 2011; 97: 1332-7.
28. Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. *Eur Heart J* 2001; 22: 22-36.
29. Jasaityte R, Claus P, Teske AJ, Herbots L, Verheyden B, Jurcut R, et al. The slope of the segmental stretch-strain relationship as a noninvasive index of LV inotropy. *JACC Cardiovasc Imaging* 2013; 6: 419-28.

30. Palardy M, Ducharme A, O'Meara E. Inhibiting the renin-angiotensin system with ACE Inhibitors or ARBs after MI. *Curr Heart Fail Rep* 2007; 4: 190-7.

## **Relation entre gradient de pression intraventriculaire diastolique et remodelage ventriculaire gauche**

Un grand nombre d'études ont évalué la valeur prédictrice de paramètres échocardiographiques pour la survenue d'un RVG en post-infarctus. Il a ainsi été montré que le strain longitudinal global [55, 56, 74], le *wall motion score index* (évaluant la qualité de la contraction myocardique segmentaire) [56, 74, 75] et certains paramètres de rotation et de twist [57, 74, 75] sont associés à la survenue d'un RVG après SCA. En revanche, les données de la littérature sont moins formelles concernant la valeur prédictrice de l'évolution vers un RVG des paramètres de fonction diastolique comme le volume de l'OG [55, 76], le ratio  $\frac{E}{A}$  [55, 75, 77], le temps de décélération de l'onde E [76, 77] ou encore le ratio  $\frac{E}{\rho}$  [75, 76].

Une dysfonction diastolique est retrouvée dans un grand nombre de pathologies cardiovasculaires, y compris l'infarctus du myocarde, et est associée à une augmentation du risque de réhospitalisation au décours de l'épisode initial [78, 79]. La dysfonction diastolique précède parfois l'altération de la fonction systolique VG, conduisant à des symptômes d'IC chez des patients ayant une FEVG préservée [80]. La détorsion du VG est un mécanisme important de la fonction diastolique [81]. La contraction du VG puis la phase de relaxation active qui suit en début de diastole a pour conséquence la création d'une hétérogénéité de pression au sein de ce dernier. Ce gradient de pression négatif entre la valve mitrale et l'apex du VG est responsable d'un phénomène de succion qui va aspirer le sang de l'OG vers le VG en début de diastole [82]. Il a été précédemment montré que ce gradient de pression est corrélé aux indices de relaxation VG [83, 84], en faisant ainsi un paramètre d'évaluation de la fonction diastolique. Il a été montré que l'échocardiographie en mode

TM avec Doppler couleur permet la quantification non invasive de ce gradient de pression intraventriculaire diastolique (GPIVD), aussi bien dans les études précliniques que chez l'homme [85, 80, 86]. De nombreuses situations sont susceptibles de diminuer le GPIVD parmi lesquelles l'ischémie myocardique [87]. En revanche, la relation entre GPIVD et RVG n'est pas connue. Nous avons donc étudié l'association entre le GPIVD à la phase aiguë de l'infarctus et la survenue d'un RVG lors du suivi chez des patients pris en charge pour un STEMI, traités par angioplastie coronaire et sans signe clinique d'IC.

## **Matériels et Méthodes**

### *Sélection des patients*

Cette étude est une étude prospective, observationnelle ayant inclus des patients consécutivement admis pour STEMI et traités soit par angioplastie primaire soit par fibrinolyse puis angioplastie coronaire, entre juin 2015 et octobre 2018. Les critères d'inclusion sont: âge  $\geq 18$  ans, douleur datant de moins de 12 heures, présence d'un sus-décalage du segment ST sur l'électrocardiogramme qualifiant. Les critères d'exclusion sont: revascularisation incomplète (persistance d'une sténose résiduelle  $>30\%$  en regard de la lésion coupable et/ou score TIMI  $<3$ ), signes cliniques d'IC définis par une classe Killip  $\geq II$ , fibrillation atriale, pathologie responsable d'une espérance de vie estimée à moins de 12 mois ou suivi planifié dans un autre établissement. Un consentement éclairé écrit a été recueilli pour tous les patients et le protocole a été approuvé par le Comité de Protection des Personnes Nord-Ouest III.

*Échocardiographie*

Une échocardiographie cardiaque 3D est réalisée chez tous les patients dans les 48 heures suivant l'admission et à 6 mois, au moyen d'un échocardiographe EPIQ 7G (Philips Healthcare, Best, Pays-Bas), équipé d'une sonde 1 à 5-MHz (XMATRIX X5-1). Les acquisitions sont réalisées en décubitus latéral gauche et en apnée, durant 3 cycles cardiaques. Le volume télédiastolique (VTD) et le volume télésystolique (VTS) VG sont mesurés à partir des acquisitions 3D et normalisés par la surface corporelle [88]. Le volume de l'OG est mesuré selon la méthode biplan en télésystole et est également normalisé à la surface corporelle. La fonction diastolique est mesurée selon les recommandations actuelles ASE/EACVI [72], comprenant la quantification de l'onde E et de l'onde A sur le flux Doppler transmitral, la mesure du pic de vitesse de l'anneau mitral ( $e'$ ) en doppler tissulaire (moyenne des pics en septal et en latéral). L'existence d'un RVG au cours du suivi est défini par une augmentation  $\geq 20\%$  du VTD par rapport à sa valeur initiale [89]. La quantification de ces paramètres sont réalisés au décours de l'examen, sur une station dédiée, par deux opérateurs indépendants, au moyen des logiciels Intellispace Cardiovascular [Philips Healthcare, Best, Pays-Bas], TomTec [TomTec Imaging Systems GmbH, Unterschlessheim, Allemagne] et un programme dédié au calcul du GPIVD développé dans Matlab [version R2020a].

*Quantification du gradient de pression intraventriculaire diastolique*

Le flux à travers une valve mitrale normale peut être étudié par l'équation de Navier-Stokes pour les fluides incompressibles, la masse volumique du sang ne dépendant pas de la pression ou de la température dans les conditions d'acquisition [80]. La composante gravitationnelle peut être négligée, de même que la composante visqueuse, considérant que le flux observé en doppler couleur n'est pas au contact des parois valvulaires. Si on considère

ensuite l'analyse d'un flux le long de la ligne Doppler, on aboutit alors à l'équation d'Euler (équation 1) où  $P$  représente la pression,  $v$  la vitesse Doppler,  $s$  la coordonnée le long de l'axe TM,  $t$  le temps et  $\rho$ , la masse volumique du sang.

$$\frac{\partial P}{\partial s} = -\rho \left[ \frac{\partial v}{\partial t} + v \frac{\partial v}{\partial s} \right] \quad (1)$$

L'intégration de cette équation fait apparaître plus clairement les deux composantes restantes à la variation de pression : la composante convective et la composante inertielle (respectivement en bleu et en rouge dans l'équation 2, équation de Bernoulli) [85]. La composante convective correspond à la perte de pression consécutive à l'augmentation de l'énergie cinétique quand le flux passe à travers un orifice. La composante inertielle correspond à la variation de pression nécessaire pour accélérer une masse de sang. Le GPIVD correspond à la somme de ces deux composantes.

$$P_{base} - P_{apex} = \frac{1}{2} \rho (v_{apex}^2 - v_{base}^2) + \rho \int_{base}^{apex} \frac{\partial v}{\partial t} \partial s \quad (2)$$

Le flux mitral est enregistré en mode TM et Doppler couleur en vue apicale 4 cavités durant une brève apnée. Les données sont stockées au format Dicom, comprenant les données natives, et sont affichées au format JPEG (Joint Photographic Experts Group). Les images sont traitées au décours de l'examen par notre logiciel précédemment publié [86] afin d'estimer la différence instantanée de pression entre la base du VG et l'apex. Afin de pouvoir quantifier le GPIVD, l'alignement de l'acquisition Doppler doit être dans l'axe du flux sanguin, les structures anatomiques du VG et surtout la valve mitrale doivent être visibles et il ne doit pas y avoir d'obstruction au flux sanguin. Le logiciel est automatique permettant

d'avoir une meilleure reproductibilité inter-opérateur. En revanche, si l'utilisateur juge que le plan de l'ouverture mitrale n'est pas positionné de façon adéquate, il est possible de réajuster sa position manuellement. La résolution temporelle est définie à 75 mm/s mais peut être modifiée en fonction de la fréquence cardiaque afin d'avoir 3 cycles consécutifs et moyenner les mesures. Brièvement, le logiciel traite l'image en réalisant un désaliasing [90, 91] puis un lissage avant de pouvoir déterminer les composantes convectives et inertielles et donc le GPIVD. Un exemple du processus est représenté sur la Figure 4.

### *Analyse statistique*

Les variables continues sont représentées sous forme de moyenne  $\pm$  écart-type ou médiane et espace interquartile selon la distribution du paramètre. Les variables qualitatives sont présentées sous forme de nombre et pourcentages. Les patients sont répartis en deux groupes selon l'existence (RVG $\oplus$ ) ou non (RVG $\ominus$ ) d'un RVG au cours du suivi. Les caractéristiques de ces deux groupes sont comparées par le test  $t$  de Student ou le test de Mann-Whitney. Nous avons utilisé des modèles de régression linéaire et logistique pour étudier la relation entre l'évolution des volumes VG en tant que variable continue et l'existence d'un RVG en tant que variable binaire respectivement et les paramètres échocardiographiques à la phase initiale. Ces analyses ont été réalisées sans ajustement et après ajustement sur les VTD et VTS initiaux. Le logiciel utilisé est R version 3.6.3 (R Foundation for Statistical Computing, Vienne, Autriche). Les tests utilisés sont bilatéraux avec un seuil de significativité fixé à 0,05.

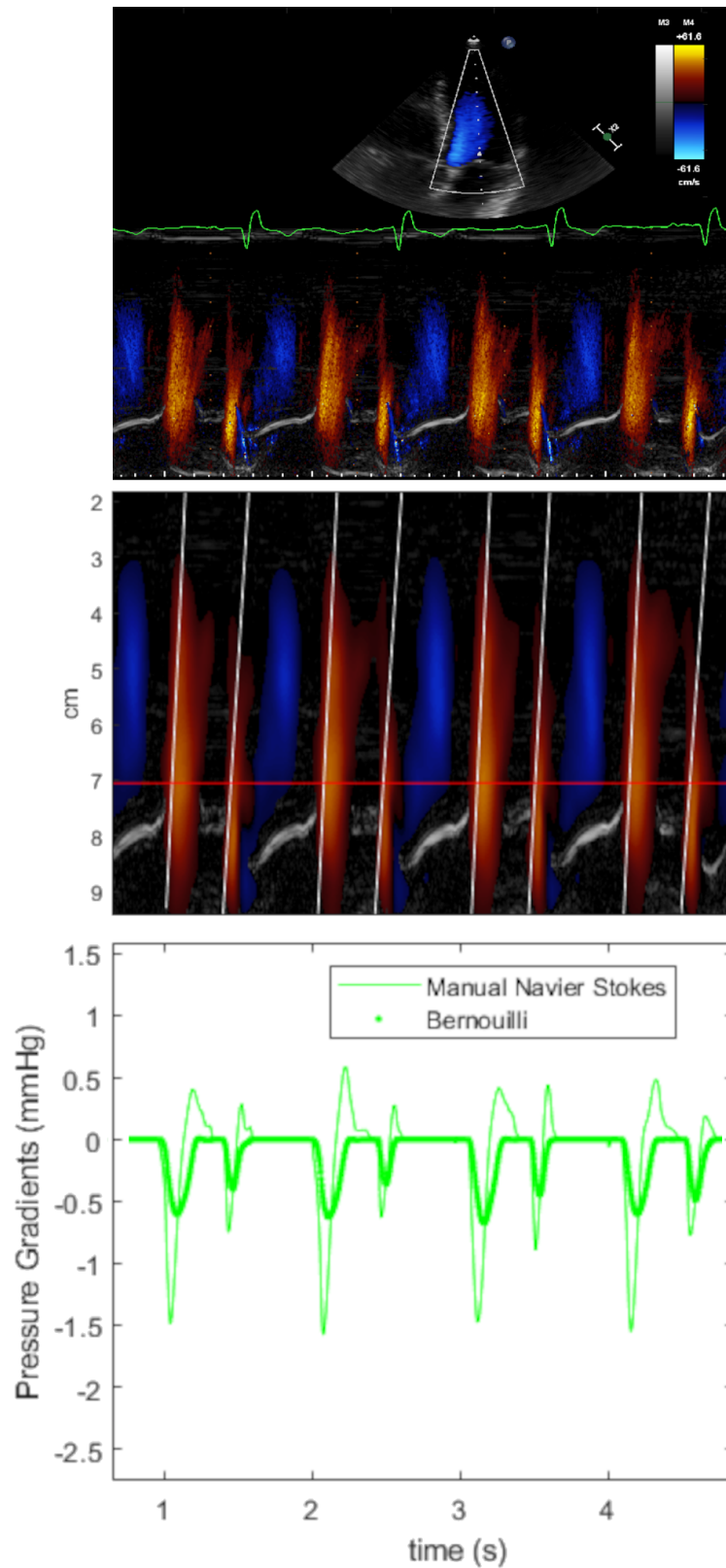


Fig. 4 **Mesure du gradient de pression intraventriculaire diastolique.** En haut: image TM doppler couleur centré sur le flux mitral, vitesse de défilement: 75mm/s. Au milieu: traitement de l'image (désaliasing et lissage). En bas: courbe de valeur du gradient de pression intraventriculaire diastolique (équation de Navier Stokes): -1,4 à -1,5 mmHg selon les mesures.

## Résultats

### *Population de l'étude*

Parmi les 205 patients qui ont eu une échocardiographie complète à la phase initiale de l'infarctus, 4 sont décédés au cours du suivi, avant la réalisation de la seconde échocardiographie. Trente-neuf patients n'ont pas été revus au décours de l'hospitalisation initiale, majoritairement en raison d'un suivi organisé en dehors du centre (Figure 5). Enfin, 29 patients ont été rétrospectivement exclus en raison d'une qualité insuffisante des acquisitions échocardiographiques (TM avec Doppler couleur ou acquisition 3D pour la mesure des volumes VG). Les caractéristiques des 133 patients inclus dans l'analyse sont décrites dans la Table 3. L'âge moyen est de 56,9 ans [49,4 – 67,5] et 113 (85%) sont de sexe masculin. La durée médiane entre le début de la symptomatologie et la revascularisation coronaire est de 4,1 heures [2,9 – 7,0].

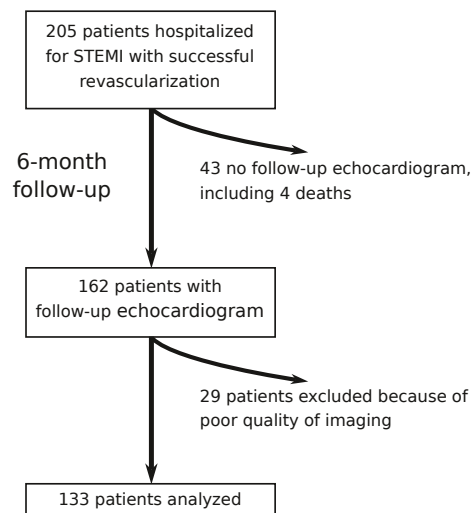


Fig. 5 Flow chart.

Table 3 : Caractéristiques de la population.

|                                            | Population<br>générale | LVR $\oplus$          | LVR $\ominus$         | valeur<br>de p |
|--------------------------------------------|------------------------|-----------------------|-----------------------|----------------|
|                                            | n=133                  | n=38                  | n=95                  |                |
| Age, années                                | 56,9 [49,4 – 67,5]     | 62,5 [50,9 – 68,8]    | 56,0 [49,3 – 66,8]    | 0,41           |
| Sexe masculin                              | 113 (85,0%)            | 35 (92,1%)            | 78 (82,1%)            | 0,24           |
| Hypertension artérielle                    | 48 (36,1%)             | 12 (31,6%)            | 36 (37,9%)            | 0,63           |
| Diabète de type 2                          | 20 (15,0%)             | 7 (18,4%)             | 13 (13,7%)            | 0,68           |
| Hypercholestérolémie                       | 53 (39,8%)             | 19 (50,0%)            | 34 (35,8%)            | 0,19           |
| Tabagisme                                  | 83 (62,4%)             | 22 (57,9%)            | 61 (64,2%)            | 0,63           |
| IMC, kg/m <sup>2</sup>                     | 26,1 [24,2 – 29,0]     | 26,0 [24,6 – 27,4]    | 26,2 [24,0 – 29,1]    | 0,44           |
| Délai de reperfusion <sup>†</sup> , heures | 4,1 [2,9 – 7,0]        | 4,0 [3,3 – 6,7]       | 4,2 [2,9 – 7,9]       | 0,84           |
| Infarctus antérieur                        | 57 (42,9%)             | 16 (42,1%)            | 41 (43,2%)            | 1              |
| <i>A l'admission</i>                       |                        |                       |                       |                |
| FC, bpm                                    | 75 $\pm$ 17            | 73 $\pm$ 19           | 75 $\pm$ 17           | 0,57           |
| PAS, mmHg                                  | 140 [119 – 156]        | 133 [115 – 150]       | 141 [119 – 159]       | 0,43           |
| PAD, mmHg                                  | 80 [70 – 94]           | 80 [66 – 89]          | 80 [70 – 97]          | 0,26           |
| DFG estimé, mL/min/1,73 m <sup>2</sup>     | 93 [80 – 106]          | 88 [77 – 101]         | 97 [80 – 107]         | 0,17           |
| <i>Echocardiographie initiale</i>          |                        |                       |                       |                |
| VTD indexé, mL/m <sup>2</sup>              | 57,9 [47,7 – 66,3]     | 56,8 [47,4 – 66,3]    | 58,0 [47,8 – 66,3]    | 0,78           |
| VTS indexé, mL/m <sup>2</sup>              | 30,6 [24,6 – 37,4]     | 32,8 [24,8 – 38,2]    | 28,7 [24,6 – 34,8]    | 0,19           |
| FEVG, %                                    | 46,5 [40,1 – 53,2]     | 42,9 [37,8 – 47,8]    | 48,3 [41,0 – 53,8]    | <0,01          |
| Rapport $\frac{E}{A}$                      | 0,96 [0,83 – 1,18]     | 0,98 [0,85 – 1,18]    | 0,96 [0,79 – 1,17]    | 0,53           |
| Temps de décélération de l'onde E, ms      | 200 [170 – 235]        | 180 [153 – 230]       | 200 [170 – 240]       | 0,046          |
| Rapport $\frac{E}{e'}$ moyen               | 8,1 [7,0 – 9,9]        | 8,1 [6,7 – 9,3]       | 8,1 [7,1 – 9,9]       | 0,75           |
| Volume de l'OG, mL/m <sup>2</sup>          | 31,4 [26,4 – 37,6]     | 32,0 [27,3 – 39,0]    | 31,2 [26,2 – 37,5]    | 0,41           |
| GPIVD (valeurs absolues), mmHg             | 1,28 [0,96 – 1,85]     | 1,26 [1,02 – 1,95]    | 1,28 [0,92 – 1,85]    | 0,52           |
| <i>Echocardiographie de suivi</i>          |                        |                       |                       |                |
| VTD indexé, mL/m <sup>2</sup>              | 59,2 [49,8 – 71,7]**   | 83,0 [67,1 – 92,1]*** | 54,9 [47,5 – 64,9]*   | <0,001         |
| VTS indexé, mL/m <sup>2</sup>              | 27,5 [21,1 – 40,2]     | 43,0 [35,0 – 52,9]*** | 23,8 [19,7 – 30,5]*** | <0,001         |
| FEVG, %                                    | 52,1 [44,2 – 57,1]***  | 47,1 [41,6 – 51,1]    | 54,0 [47,1 – 59,6]*** | <0,01          |

DFG, débit de filtration glomérulaire ; FC, fréquence cardiaque ; FEVG, fraction d'éjection ventriculaire gauche ; GPIVD, gradient de pression intraventriculaire diastolique ; IMC, indice de masse corporelle ; OG, oreillette gauche ; PAD, pression artérielle diastolique ; PAS, pression artérielle systolique ; VTD, volume télédiastolique ; VTS, volume télésystolique. <sup>†</sup>délai compris entre le début de la symptomatologie et la revascularisation (succès de fibrinolyse, angioplastie primaire ou de sauvetage) \*p<0,05 ; \*\*p<0,01 ; \*\*\*p<0,001.

*Volumes et fonction du ventricule gauche*

Trente-huit patients (28,6%) ont présenté un RVG au cours du suivi. Il n'y a pas de différence entre les groupes LVR $\oplus$  et LVR $\ominus$  concernant les valeurs initiales de VTD indexé (56,8 mL/m<sup>2</sup> [47,4 – 66,3] et 58,0 mL/m<sup>2</sup> [47,8 – 66,3] respectivement ; p=0,78 ; Table 3) et de VTS indexé (32,8 mL/m<sup>2</sup> [24,8 – 38,2] et 28,7 mL/m<sup>2</sup> [24,6 – 34,8] ; p=0,19). En revanche, les patients du groupe LVR $\oplus$  ont une FEVG plus basse lors de l'échocardiographie initiale (42,9% [37,8 – 47,8] et 48,3% [41,0 – 53,8] respectivement ; p<0,01). Lors de l'échocardiographie de suivi, les valeurs de VTD et VTS sont plus élevées dans le groupe LVR $\oplus$ , comme attendu (83,0 mL/m<sup>2</sup> [67,1 – 92,1] et 54,9 mL/m<sup>2</sup> [47,5 – 64,9] ; p<0,01 pour le VTD et 43,0 mL/m<sup>2</sup> [35,0 – 52,9] et 23,8 mL/m<sup>2</sup> [19,7 – 30,5] ; p<0,001 pour le VTS). La FEVG augmente significativement dans le groupe LVR $\ominus$  lors du suivi mais pas dans le groupe LVR $\oplus$  (p<0,001 et p=0,12 respectivement).

*Paramètres de fonction diastolique*

Le temps de décélération de l'onde E mitrale est plus long dans le groupe LVR $\ominus$  par rapport au groupe LVR $\oplus$  (200 ms [170 – 240] et 180 ms [153 – 230] ; p<0,05). Le rapport  $\frac{E}{A}$  est similaire dans les deux groupes (0,98 [0,85 – 1,18 dans le groupe LVR $\oplus$  et 0,96 [0,79 – 1,17] dans le groupe LVR $\ominus$  ; p=0,53). Il n'existe pas de différence du rapport  $\frac{E}{a}$  entre les groupes (8,1 [6,7 – 9,3] dans le groupe LVR $\oplus$  et 8,1 [7,1 – 9,9] dans le groupe LVR $\ominus$  ; p=0,75).

*Relations entre le gradient de pression intraventriculaire diastolique, les paramètres de fonction diastolique et le remodelage ventriculaire gauche*

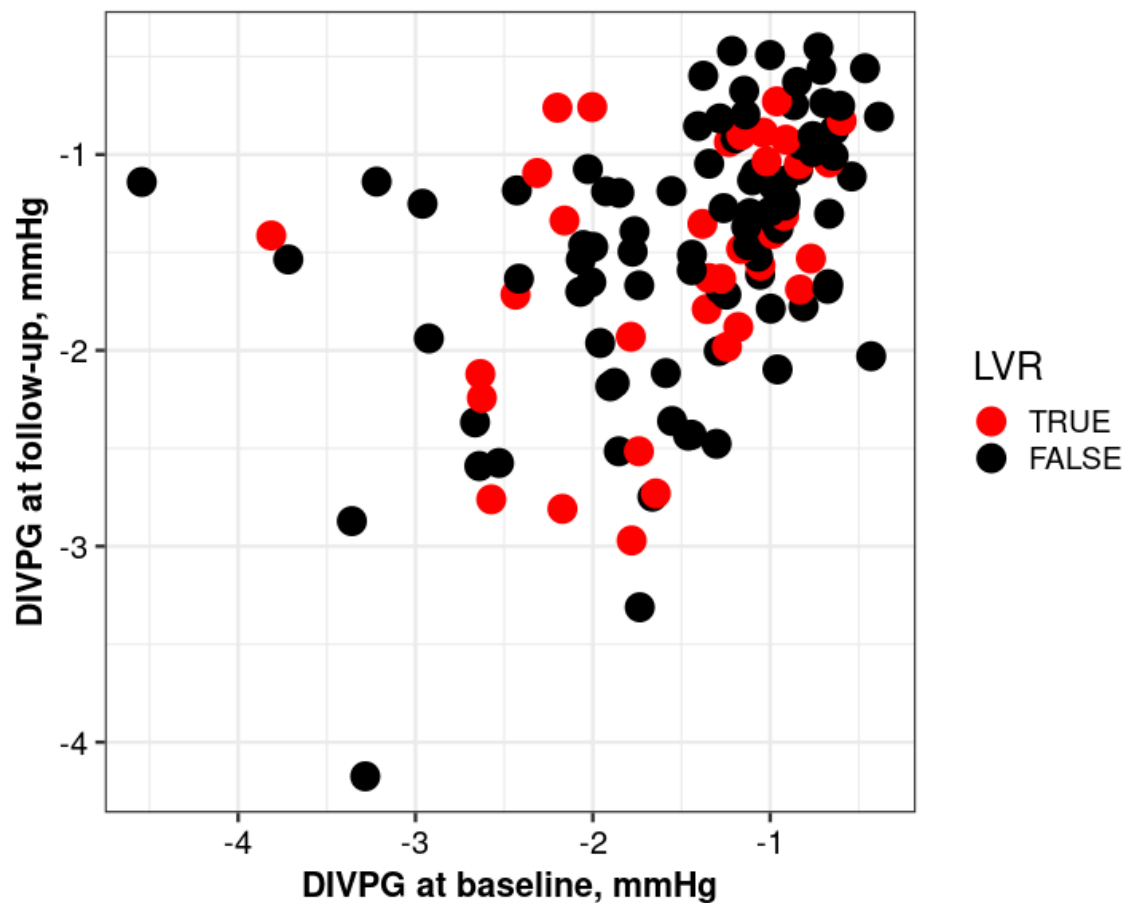
Le gradient de pression intraventriculaire diastolique est similaire dans les deux groupes lors de l'examen initial (1,26 mmHg [1,02 – 1,95] dans le groupe LVR $\oplus$  et 1,28 mmHg [0,92 – 1,85] dans le groupe LVR $\ominus$  ; p=0,52). Ce résultat est retrouvé même après ajustement

sur la FEVG ou les volumes VG initiaux. Nous n'avons pas retrouvé de relation entre la variation du GPIVD et la variation de la FEVG ( $p=0,56$ ) ou le RVG ( $p=0,72$ ) au cours du suivi (Figure 6). Il existe une corrélation significative entre le GPIVD et les paramètres de fonction diastolique mesurés sur l'échocardiographie initiale, et notamment: (i) le rapport  $\frac{E}{A}$  ( $r=-0,26$  ;  $p<0,01$ ) ; (ii) le rapport  $\frac{E}{e'}$  ( $r=-0,24$  ;  $p<0,01$ ) et (iii) le pic de vélocité de l'onde E mitrale ( $r=0,63$  ;  $p<0,001$  ; Figure 7). Concernant la relation entre le GPIVD et la fonction diastolique, il existe une tendance non significative à une valeur plus faible (en valeur absolue) du GPIVD chez les patients ayant une dysfonction diastolique de grade 1 par rapport à ceux ayant une dysfonction diastolique de grade indéterminé (1,15 mmHg [0,88 – 1,75] et 1,39 mmHg [1,05 – 2,00] respectivement ;  $p=0,07$  ; Figure 8).

### Discussion

Notre étude n'a pas permis de montrer d'association significative entre le GPIVD calculé sur l'échocardiographie initiale et la survenue d'un RVG au cours du suivi. En revanche, il existe une association entre le GPIVD et certains paramètres de fonction diastolique, notamment le pic de vélocité de l'onde E mitrale mais aussi dans une moindre mesure les rapports  $\frac{E}{A}$  et  $\frac{E}{e'}$ . Il existe également une tendance pour une relation entre GPIVD et le grade de dysfonction diastolique.

Le remplissage VG est un phénomène complexe qui dépend de plusieurs paramètres : la relaxation des fibres myocardiques, la pression de l'OG et sa contractilité, la pression du VG en fin de diastole, sa fonction systolique et sa compliance [81]. La détorsion du VG durant la phase de relaxation isovolumique est un mécanisme-clé du remplissage VG précoce. Le retour du VG à sa conformation pré-éjection permet de libérer l'énergie stockée lors de la systole dans les éléments élastiques du tissu [81, 92] et contribue à générer un gradient de



**Fig. 6 Relation entre la variation du gradient de pression intraventriculaire diastolique et le remodelage ventriculaire gauche au cours du suivi.** Le remodelage ventriculaire gauche (LVR) est défini par une augmentation  $\geq 20\%$  du volume télédiastolique au cours du suivi.

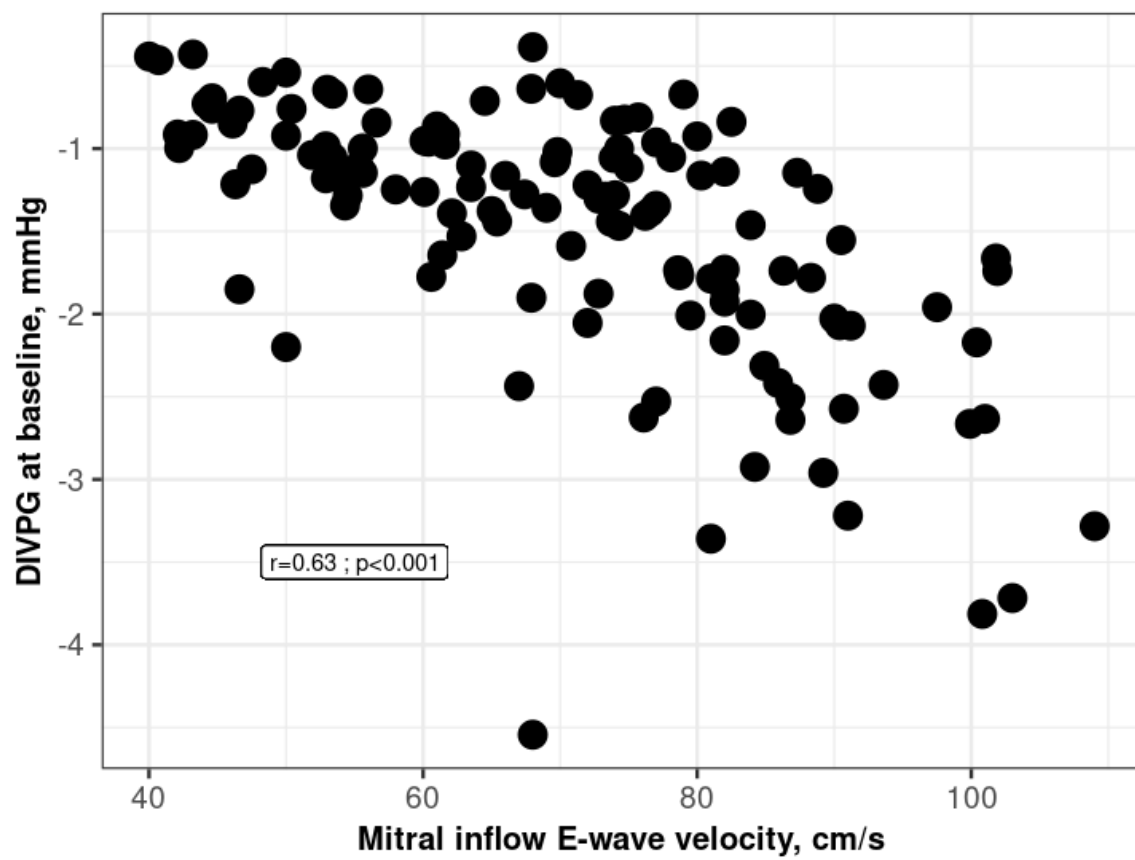


Fig. 7 Relation entre le gradient de pression intraventriculaire diastolique et le pic de vélocité de l'onde E mitrale.

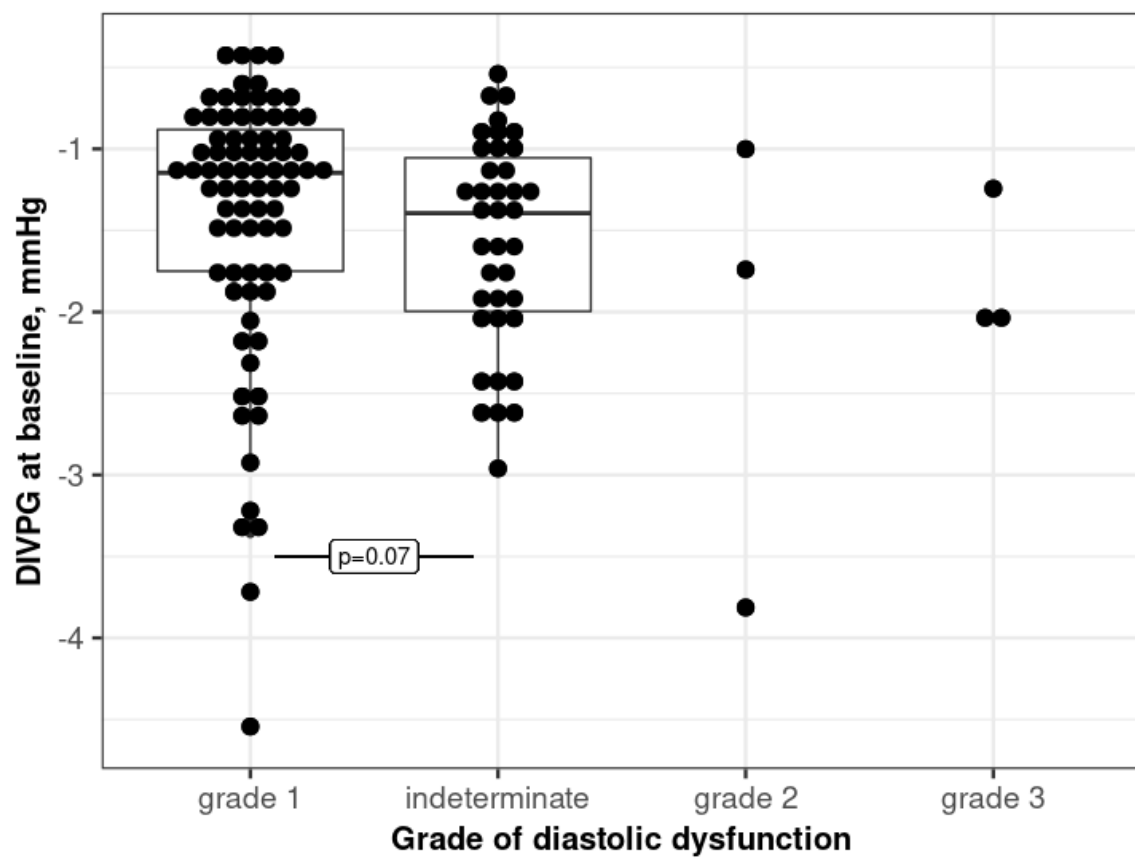


Fig. 8 Relation entre le gradient de pression intraventriculaire diastolique et le grade de dysfonction diastolique.

pression intraventriculaire qui va créer une succion du sang vers le VG. Ce gradient est mesurable de façon non-invasive [86].

Dans notre étude, le GPIVD moyen est de 1,28 mmHg [0,96 – 1,85] dans les 24 à 48 heures suivant le STEMI, en utilisant une acquisition TM centrée sur la valve mitrale et la fonction Doppler couleur. Notre équipe a mis en évidence des valeurs de GPIVD plus élevées chez des volontaires sains (3,2 mmHg  $\pm$  1,0 mmHg) [86]. Plusieurs explications peuvent être avancées pour expliquer cette différence. Premièrement, il a été mis en évidence dans des études précliniques que l'ischémie est une situation qui diminue le GPIVD [87]. Il existe des modifications marquées du profil de remplissage dans des situations comme l'ischémie myocardique ou l'IC, que ce soit dans des études précliniques [83, 93] ou chez l'homme [84]. Deuxièmement, la rigidité du VG augmente avec l'âge et les patients que nous avons inclus sont plus âgés que dans la littérature [94]. Troisièmement, un facteur déterminant du remplissage VG est sa fonction systolique. Les anomalies régionales de la fonction systolique VG que l'on observe dans l'infarctus du myocarde va induire une diminution de l'énergie stockée durant la systole et donc une diminution de l'énergie relâchée en début de diastole [87], diminuant ainsi le GPIVD. Aussi, il a été proposé que les anomalies de la torsion du VG conduise à une augmentation de la demande en oxygène par un mécanisme de diminution de l'efficacité de la contraction myocardique (par une perte de l'uniformité du stress sur les fibres myocardiques [95]). Cette augmentation de la demande en oxygène toucherait alors également les zones *remote* du myocarde et conduirait à terme à une altération de la contractilité et au RVG [96].

Il existe des données contradictoires dans la littérature sur l'association entre la torsion VG et le RVG. La torsion VG mesurée à la phase aiguë n'est pas associée à la survenue d'un RVG chez 75 patients avec STEMI antérieur [75]. Une autre étude a montré que les

patients ayant présenté un RVG au cours du suivi ont des paramètres plus bas de torsion VG au décours immédiat de l'infarctus [97]. Dans cette même étude, il existe une association significative entre FEVG et torsion VG, qui n'est pas retrouvée comme un facteur prédictif indépendant de RVG. D'autres auteurs ont montré que la torsion VG est associée significativement à la FEVG et à la taille de l'infarctus mais aussi au RVG, en analyse multivariée [74]. Il existe moins de données sur la relation entre la détorsion du VG et le RVG. Dans une étude ayant inclus 208 patients avec STEMI mais avec une FEVG et des paramètres de torsion VG meilleurs que dans l'étude précédente, les paramètres de détorsion ne sont pas associés à la survenue d'un RVG au cours du suivi [76].

Il existe également des données divergentes sur la valeur prédictrice des paramètres plus conventionnels de fonction diastolique quant à la survenue d'un RVG au décours d'un STEMI. Il n'existe pas d'association entre un profil restrictif du remplissage VG et la survenue d'un RVG chez 109 patients pris en charge pour un STEMI [98]. En revanche, la mise en évidence d'un profil restrictif – défini par un temps de décélération de l'onde E mitrale  $\leq 130$  ms – est associé à l'absence de survenue d'un remodelage "reverse", défini dans l'étude par une diminution  $>10\%$  du VTS VG dans une population de 184 patients, à 6 mois de l'épisode initial [99]. Dans une étude post-hoc de l'étude TIPTOP, une dysfonction diastolique de grade 3, définie par un rapport  $\frac{E}{A} \geq 2$  conformément aux recommandations en vigueur [72], est associée à une plus grande augmentation du VTS et une moindre amélioration de la FEVG au cours du suivi [100]. Le GPIVD n'est pas associé à la survenue d'un RVG dans notre étude. Il existe des différences entre l'étude post-hoc de TIPTOP précédemment citée et la notre qui peuvent expliquer ces résultats. Premièrement, nous avons inclus un nombre limité de patients. Deuxièmement, les patients inclus dans leur étude ont une fonction systolique VG plus altérée que dans notre population [100]. La FEVG médiane est de 39% [32 – 44] dans le groupe doxycycline et 37% [33 – 43] dans le groupe contrôle de cet essai randomisé contre

46,5% [40,1 – 53,2] dans notre étude. Leur cohorte a également une fonction diastolique plus altérée. Près de deux tiers de leurs patients ont une dysfonction diastolique de grade 3, synonyme d'élévation de la pression OG alors que ce type de profil mitral est retrouvé chez seulement 3 de nos patients (2,4%). Nous avons observé que le GPIVD est plus bas chez les patients ayant une dysfonction diastolique de grade 1 et est corrélé avec le pic de vélocité de l'onde E mitrale. Une précédente étude a montré des résultats similaires, où le GPIVD est plus bas chez les patients ayant une dysfonction diastolique de grade 1 par rapport aux patients ayant une dysfonction diastolique de grade 2 ou 3 [84]. Étant donné ces résultats d'une part et l'observation de valeurs plus élevées de GPIVD chez des sujets sains d'autre part, il est possible de faire l'hypothèse que la relation entre les grades de fonction diastolique et le GPIVD suit une courbe en J, similaire à celle du rapport  $\frac{E}{A}$ . En effet, les patients ayant une dysfonction diastolique de grade 1 ont un rapport  $\frac{E}{A}$  plus bas que les patients sans anomalie de la fonction diastolique ou avec une dysfonction diastolique de grade 2 [72]. Ceci peut expliquer les résultats discordants concernant la valeur prédictive du rapport  $\frac{E}{A}$  pour la survenue d'un RVG au décours d'un STEMI. En effet, l'existence – ou non – d'une association dépend de la typologie des patients inclus. Une étude a inclus 964 patients avec STEMI et une FEVG moyenne de  $47\% \pm 9\%$ . Le rapport  $\frac{E}{A}$  est de 0,88 [0,69 – 1,10] dans le sous-groupe de patients ayant présenté un remodelage ventriculaire et 0,92 [0,75 – 1,10] dans le sous-groupe de patients sans RVG (association négative ;  $p=0,04$ ) [101]. À l'inverse, une association positive est décrite dans une autre étude ayant inclus 194 patients [102]. L'âge moyen des patients inclus est similaire mais la FEVG à l'inclusion est de  $60\% \pm 11\%$  et le rapport  $\frac{E}{A}$  est de  $1,2 \pm 0,8$  dans la population de patients ayant présenté un RVG contre  $1,1 \pm 0,4$  dans le reste de la population ( $p=0,005$ ). Étant donné que le GPIVD est corrélé au pic de vélocité de l'onde E mitrale dans notre étude, il est possible

que l'inclusion de patients ayant un grade de dysfonction diastolique plus élevé que ceux que nous avons inclus aurait conduit à des résultats différents de ceux que nous avons observé.

Ainsi, les données contradictoires de la littérature concernant l'association entre les paramètres de fonction diastolique – dont le GPIVD – et le RVG est probablement à mettre en rapport avec l'hétérogénéité des populations incluses dans les différentes études. En effet, ces paramètres de fonction diastolique ne sont pas associés à l'existence d'un RVG dans le suivi quand les patients inclus ont une FEVG relativement conservée, un faible grade de dysfonction diastolique et donc des pressions non élevées dans l'OG [76, 103]. A l'inverse, une association entre paramètres de fonction diastolique et RVG est retrouvée dans les études ayant inclus des patients ayant une altération de la FEVG ou une atteinte plus sévère de la fonction diastolique [74, 100, 55].

Notre étude présente plusieurs limites. Tout d'abord, notre population est petite et sélectionnée dans la mesure où nous avons inclus uniquement des patients revascularisés à la phase aiguë et sans signe clinique d'insuffisance cardiaque lors de l'hospitalisation initiale. Nos résultats ne peuvent donc pas être extrapolés à l'ensemble des patients pris en charge pour un STEMI. Il existe par ailleurs une variabilité de la mesure du GPIVD selon le logiciel et le matériel utilisés [82]. Cette information doit être prise en compte lors de la comparaison des valeurs de GPIVD entre différentes cohortes. Enfin, la méthodologie d'acquisition des images n'est pas standardisée. La majeure partie des acquisitions des images échocardiographiques a eu lieu entre 2016 et 2018, sans standardisation de la vitesse de défilement de l'image ou du gain. Or, il a récemment été démontré que plus le gain de l'image est augmenté, plus l'enveloppe du Doppler couleur est réduite et ceci, de façon très significative [82]. Dans

la mesure où le logiciel que nous avons utilisé travaille à partir de l'image JPEG, l'absence de standardisation du gain doit nous conduire à interpréter avec prudence les mesures de GPIVD.

### **Conclusion**

Notre étude a montré que dans une population de patients revascularisés à la phase aiguë d'un STEMI et sans signe clinique d'IC, la quantification du GPIVD, un paramètre associé à la détorsion VG, n'est pas associé à la survenue d'un RVG au cours du suivi. Avant de généraliser ces résultats à l'ensemble des patients pris en charge pour un STEMI, il est nécessaire d'étudier la relation entre le GPIVD, les paramètres de fonction diastolique et la survenue d'un RVG dans une population non sélectionnée de patients hospitalisés pour STEMI et en utilisant une méthodologie standardisée.

# **Axe biomarqueurs et remodelage ventriculaire gauche en post-infarctus**

## **Biomarqueurs et remodelage ventriculaire gauche : revue de la littérature**

De très nombreux biomarqueurs ont été décrits comme pouvant potentiellement prédire la survenue du RVG au décours d'un STEMI. Ces biomarqueurs d'intérêt avaient été colligés dans une publication lilloise, parue en 2012 [104]. Les auteurs avaient sélectionné 59 publications, concernant 52 biomarqueurs différents. Depuis, de très nombreux travaux ont porté sur cette même thématique. Avant toute nouvelle étude sur le sujet, il paraissait donc licite de refaire un point sur les données précédemment acquises.

Au total, nous avons retrouvé 134 publications décrivant 457 relations concernant plus d'une centaine de biomarqueurs différents. Parmi ces biomarqueurs, certains ont été étudiés à plusieurs reprises avec des résultats reproductibles quant à leur capacité à prédire le RVG au cours du suivi. Il s'agit surtout des marqueurs de nécrose myocardique, des peptides natriurétiques, ou encore des marqueurs d'inflammation ou des molécules intervenant sur la matrice extracellulaire. Ces biomarqueurs d'intérêt s'inscrivent donc dans la physiopathologie du RVG après SCA telle que nous l'avons brièvement rappelée au début de ce manuscrit (partie Introduction, page 2).

Ce travail montre également trois autres résultats. Premièrement, il existe une grande quantité de marqueurs biologiques décrits comme étant associés à la survenue d'un RVG au cours du suivi. Ces biomarqueurs ne sont pas réalisés en routine et les résultats manquent souvent de reproductibilité, le caractère prédictif d'un biomarqueur particulier étant souvent l'apanage d'une seule étude. Deuxièmement, un grand nombre de ces études sont des petites cohortes (le nombre médian de patients est de 88). Troisièmement, l'hétérogénéité des résultats obtenus pour certains biomarqueurs est potentiellement en rapport avec les modalités de prélèvement et de sa quantification. Le délai entre l'occlusion coronaire et le prélèvement sanguin servant à mesurer le biomarqueur doit être défini pour chaque biomarqueur, en fonction du mécanisme qu'il étudie dans la physiopathologie du SCA.

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The relationship between circulating biomarkers and left ventricular remodeling after myocardial infarction: an updated review.

Soumis à Disease Markers.

Les données supplémentaires de cet article sont disponibles dans les annexes, page 192.

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## **The relationship between circulating biomarkers and left ventricular remodeling after myocardial infarction: an updated review**

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**ABSTRACT**

Left ventricular remodeling (LVR) is common in patients with ST-elevation myocardial infarction (STEMI) and is associated with worse outcomes. Numerous clinical, imaging and biological parameters have been proposed as prognostic factor for the existence of LVR after STEMI. We performed a systematic review of the published evidence about the association of biomarkers with LVR after STEMI. Overall, 131 publications investigating 452 relations were studied. Some biomarkers were more likely to be associated with LVR at follow-up: infarct size-related biomarkers, natriuretic peptides levels (especially at discharge), white blood cells count, C-reactive protein or high-sensitivity C-reactive protein and matrix metalloproteinase-9, reflecting myocardial damage, inflammation, neurohormonal activation or matrix turnover, which are important drivers of LVR. Additionally, we found numerous articles about the relationship between 64 biomarkers that are not assessed routinely and LVR. A significant proportion of these studies showed a significant correlation but these isolated data have to be confirmed in further studies. To note, there is a high heterogeneity in the literature regarding LVR definition, timeframe of the follow-up imaging session or timing of the blood samples. The latter point is particularly important, depending of the pathophysiology of the studied biomarker. Some biomarkers reflecting myocardial damage, neurohormonal activation, inflammation and matrix turnover have been associated with LVR in past studies. Further studies using a standardized methodology to define LVR should focus on the interest of a multimarker approach to predict LVR in non-selected patients.

**KEYWORDS:** left ventricular remodeling ; acute myocardial infarction ; biomarkers ; ST-elevation myocardial infarction

## INTRODUCTION

Despite major advances in coronary revascularization for ST-elevation myocardial infarction (STEMI), left ventricular remodeling (LVR) associated with mortality and heart failure (HF) remains common [1,2]. LVR is the consequence of cellular and histological modifications [3], that are induced by deleterious adaptive mechanism involving the infarcted tissue and remote myocardium [4]. LVR has been extensively studied in clinical studies, and it is now accepted that it is influenced by several factors (e.g. infarct size or neurohormonal activation). The assessment of biomarkers at the acute phase of myocardial infarction may reflect some of these mechanisms and predict LVR in STEMI patients.

Ten years ago, Fertin et al. performed a systematic overview of 59 articles about the relationship between different biomarkers and LVR after acute myocardial infarction (AMI) [5]. During the last decade, a growing number of studies brought new data about the relationship between some biomarkers and LVR. In the present study, we aim to perform an update of published evidence on the association of circulating biomarkers, assessed at the acute phase of STEMI, with LVR.

## METHODS

### Search strategy

We conducted a computerized Medline search of published articles through July 2020, using the following combined criteria: (i) (« remodeling »[Title/Abstract] OR « remodelling »[Title/Abstract] OR « volume »[Title/Abstract]) AND (ii) « myocardial infarction »[Title/Abstract]) AND (iii) (« follow-up »[Title/Abstract] or « months »[Title/Abstract] or « month »[Title/Abstract]). The third part of the combined search was set to exclude studies with no follow-up after the index STEMI. Review articles and bibliographies of all relevant articles were searched manually for additional articles. Eligible studies had to fulfil the following criteria: (i) patients were admitted with STEMI or AMI but the proportion of patients with STEMI is described, (ii) the baseline imaging session was performed within 10 days following STEMI, (iii) the follow-up imaging session was performed >1 month after STEMI, (iv) the number of included patients was  $\geq 30$ , (v) the biomarkers of interest were measured during the index admission, (vi) LVR was defined or the relationship between the biomarkers and the change regarding left ventricular volumes was available, and (vii) the article was written in English.

## Statistical analysis

We anticipated a significant heterogeneity regarding included population, timeframe of biomarkers and imaging sessions and the definition of LVR from one study to another. As a consequence, it was not possible to conduct a formal meta-analysis. The correlation between a biomarker level and LVR was defined as positive if a high level of the biomarker was significantly associated ( $p < 0.05$ ) with either the definition of LVR used in the study or with left ventricular dilation at follow-up if no definition of LVR was provided. Conversely, the correlation was defined as negative if a low level of biomarker was significantly associated ( $p < 0.05$ ) with LVR or left ventricular dilation. Otherwise, there was no correlation between the level of the biomarker and LVR.

## RESULTS

The relationship between LVR and a wide spectrum of potential biomarkers have been studied after STEMI. Unless otherwise indicated, the tables in the present document contain only data about biomarkers that have been studied more than twice in the literature, with significant association with LVR. The full dataset including isolated studies regarding a specific biomarker or biomarkers that were never associated with LVR in past studies is available as Supplementary materials. The median number of patients per study was 88 (range: 30, 1995) in the 131 selected publications. The median follow-up duration was 6 months (range: 1, 44). Forty studies (30.5%) used cardiac magnetic resonance (CMR) imaging and 85 (64.9%) used transthoracic echocardiography. Eighty-nine studies used a cut-off value for LVR (67.9%) and 5 (3.8%) defined reverse LVR as a 10 to 15% decrease in ESV during follow-up. When LVR was defined as a dichotomous criterion, the prevalence of LVR ranged from 12.5% to 51.8%. The cut-off values of a  $\geq 20\%$  increase in left ventricular end-diastolic volume and a  $\geq 15\%$  increase in left ventricular end-systolic volume were the two most common criteria (55 [42.0%] and 8 [6.0%] studies, respectively). Eighty-seven studies described a relationship between biomarkers used to assess infarct size (e.g. troponin or creatine phosphokinase) and LVR (Supplementary Table). Among the 129 associations, a positive correlation was reported in 79 cases (61.2%, and 19 were positive in multivariate analysis [14.7%]), a negative correlation in

2 cases (but related to the same publication [6]), a variable or borderline ( $p=0.05$ ) correlation in 2 cases and no correlation in 46 cases (35.7%).

### Natriuretic peptides

The 46 studies that described a relationship between natriuretic peptides and LVR are presented in Table 1. A positive association was reported in 19 studies (41.3%). Among these studies, 6 described a positive relationship in multivariate analysis whereas the association was no longer present in multivariate analysis in 5 studies. A variable association, depending of the timing of the measurement of the biomarker was described in 7 studies. The only study that reported a negative association showed no longer association in multivariate analysis. The 18 remaining studies reported no significant association between natriuretic peptides levels and LVR.

### Complete blood count, biochemistry and lipid profile

The relationship between complete blood count parameters and LVR are depicted in Table 2. Among the 6 studies that investigated the association between hemoglobin levels and LVR, only 2 studies found that there was a positive correlation between hemoglobin and LVR [47,48]. However, these studies were conducted by the same team and used a nonconventional definition of LVR ( $>20\text{mL}/\text{m}^2$  increase in EDVi, and any increase in EDVi, respectively). Regarding white blood cells, we selected 14 publications and found 17 associations. Among these associations, 4 failed to demonstrate a significant association in multivariate analysis whereas a fifth study showed that the positive association remains after multivariate analysis. The relationship between renal function and LVR has been described in 25 studies. Among these studies, only two described that low kidney function is associated with LVR at follow-up (Supplementary Table, (i) Buono et al. [60]: estimated glomerular filtration rate:  $94\pm 20\text{ mL}/\text{min}/1.73\text{m}^2$  in patients without LVR vs.  $85\pm 21\text{ mL}/\text{min}/1.73\text{m}^2$  in patients with LVR [ $p=0.032$ ], and (ii) Liu et al. [30]: OR=0.939 in both univariate [ $p<0.0001$ ] and multivariate [ $p=0.0137$ ] analysis for renal function). One third of the 15 studies described a significant positive correlation between glucose levels and LVR (Table 3). However, it is likely that there is no significant association between baseline lipid profile after STEMI and LVR as only one study showed a positive correlation between high-density lipoprotein cholesterol and LVR (Supplementary Data).

### **Inflammation, fibrosis and extracellular matrix**

The Table 4 shows the relationship between markers of inflammation and LVR. Twenty-nine studies investigated the association between inflammation markers (mainly C-reactive protein or high-sensitivity C-reactive protein) and LVR: there was no correlation in 14 cases (48.3%), a positive correlation in 9 cases (31.0%, with 3 positive correlation using multivariate analysis and 4 studies without significant relationship after multivariate or propensity-matched analysis) and a variable correlation in 2 cases, depending of the timing of the assessment of the biological parameter: no correlation at admission and positive association at 24 hours or at discharge. Regarding 14 fibrosis and extracellular matrix-related biomarkers, MMP-9 was the most investigated (Table 5). MMP-9 levels was associated with LVR as 6 studies demonstrated significant positive correlation between MMP-9 and LVR.

### **Other biomarkers**

The relationship between 64 other biomarkers (including 12 miRNA) and LVR is depicted in Supplementary Table. A significant proportion of these studies demonstrated an association between biomarker level and LVR, but it may be taken with care as most of the data of the latter studies were isolated studies. The Table 6 described data about some biomarkers that have been reported twice or more (galectin-3 [29,51], hepatocyte growth factor [76,77], myeloperoxidase [71,78,79], osteoprotegerin [80,81] and suppression of tumorigenicity-2 [33,40]).

### **DISCUSSION**

The results of the present review could be synthetized as following: (i) there is a massive literature about the relationship between circulating biomarkers and LVR in STEMI patients but there is no standardized cut-offs to define LVR and no standardized method for the assessment of biomarkers, allowing to draw definitive conclusions about the latter associations, (ii) there is data supporting that LVR is associated with baseline levels of some biomarkers related to infarct size, neurohormonal activation, inflammation, and matrix turnover and, (iii) it is of utmost importance to perform blood samples according to the pathophysiology of the biomarker of interest (e.g. biomarkers of neurohormonal activation at admission are poorly correlated to

LVR compared to discharge levels). A greater area of infarcted tissue may lead to higher levels of inflammation, a higher impairment of left ventricular function and, as a consequence, a higher neurohormonal activation to maintain adequate hemodynamics. In the end, there is higher levels of matrix turnover biomarkers due to a larger area of infarcted myocardium and LVR (Figure 1).

The timing of the blood samples is particularly important when assessing the relationship between a biomarker and LVR. After an AMI, the expression of biomarkers is time dependent and is related to the pathophysiology of the studied mechanism. As an example, the markers of cardiac injury (e.g. troponin) rapidly peak post-AMI and then taper off. Most of the studies we included investigating the relationship between troponins levels and LVR showed a positive association (Supplementary Table). These studies assessed either the peak of troponin using serial assessments or baseline troponin within 24 hours after primary percutaneous coronary intervention as an estimate of the area of myocardial infarction. Conversely, the studies that assessed myocardial damage either only at the very acute phase of STEMI (e.g. during primary percutaneous coronary intervention) [9,50,51,82] or only at discharge [30,35,83] were more likely to fail to demonstrate a significant association with LVR. Regarding natriuretic peptides, very early assessment is poorly associated with LVR [9,13,15,27,40,51,55] as its levels reflects neurohormonal activation and is enhanced by elevated intracardiac pressure. The latter phenomenon arises in the days following STEMI and, as a consequence, elevated natriuretic peptide levels at discharge [19,22,30,37,44] is a better marker of cardiac injury and neurohormonal activation and therefore a better prognostic factor of LVR. Some studies we included assessed natriuretic peptides both at baseline and at discharge and found no association between baseline natriuretic peptides levels and LVR but a positive correlation when assessing discharge levels [11,17,26,31,42,43]. The blockade of neurohormonal activation is already a key target after AMI [84]. The ability of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to reduce cardiovascular remodeling after AMI in clinical studies is well documented [85,86]. Regarding inflammation and matrix remodeling biomarkers, their ability to predict LVR at follow-up may also be variable, depending of the timing of the assays (C-reactive protein [17], matrix turnover protein levels like metalloproteinase [42,69,71], tissue inhibitor of metalloproteinase [70,71] or N-terminal type I procollagen [42]). These results are consistent with pathophysiology as inflammatory response, including neutrophils and

macrophages activation do not peak before week 1 [87]. Then, the duration and the magnitude of the inflammation and its resolution [88] and the appropriate reactive fibrosis deposition during matrix remodeling [89] are determinants of the quality of wound healing.

The Table 6 showed the relationship between biomarkers that are not used routinely and LVR. These results are useful in a hypothesis-generating approach. However, the latter results suffer from a lack of reproducibility and external validation. Conversely to conventional biochemical assays, the latter biomarkers may not have standardized methodology: (i) antibodies may be different from a kit to another one, (ii) there is no quality check as compared to routine biomarkers, (iii) interexperiment variability may occur, (iv) there is no normal value to compare with. The present review underlines that there is a need for incoming studies investigating the interest of a multimarker approach (including simple biomarkers related to infarct size, neurohormonal activation, inflammation, and matrix turnover), possibly associated with baseline clinical and imaging data, to predict LVR and improve risk stratification in non-selected STEMI patients. The upcoming studies have to avoid classical pitfalls commonly observed in the studies investigating the relationship between biomarkers and LVR in the setting of AMI. First, LVR is commonly defined as an increase of LV volumes between a baseline and a follow-up imaging session in the setting of AMI. However, the definition of LVR is highly variable regarding the timeframe of the follow-up imaging session and the used cut-off [90]. Moreover, the patients included in these studies are highly selected [90]. Second, there are some methodological issues that have to be taken into consideration. In most of the studies we included, the assessment of biomarkers levels is not the primary objective of the study at the time of the inclusion of the patients. The published results are post-hoc analysis, based on retrospective measurements in patients included prospectively. Also, the sample size of included studies was small. The overall consequence of these methodological issues is a lack of reproducibility of the results.

There are some additional limitations regarding the data we reviewed. We did not analyse the characteristics of the included patients nor the use of medications. The relationship between biomarkers and LVR may only be speculative and the impact of known or unknown covariables were not analysed. Further studies focusing on the modulation of implicated pathways may be of particular interest.

## CONCLUSION

There is growing evidence about the relationship between biomarkers and LVR in STEMI patients. Our review showed that some biomarkers reflecting myocardial damage, neurohormonal activation, inflammation and matrix turnover may be associated with LVR. Further studies should focus on the interest of a multimarker approach to predict LVR in non-selected patients in order to help to refine risk stratification and to evaluate the interest of a more aggressive therapy (e.g. neurohormonal modulation) in high-risk patients. However, it is of utmost importance to perform blood samples according to the pathophysiology of the biomarker of interest and to use a standardized methodology to define LVR.

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**Data availability:** All data generated or analysed during this study are included in this published article and its supplementary information files (Online Resource).

**Authors' contributions:** Damien Legallois extracted and analysed the data and drafted the manuscript. Amir Hodzic extracted the data. Stéphane Allouche and Paul Milliez participated in data analysis and revised the manuscript for important intellectual content. Farzin Beygui designed the study, analysed the data and revised the manuscript for important intellectual content.

## REFERENCES

- 1 Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP,  
2 Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM,  
3 Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group.  
4 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019; 40: 87-165.  
5  
6 <https://doi.org/10.1093/eurheartj/ehy394>  
7
- 8  
9  
10  
11  
12  
13 2 van der Bijl P, Abou R, Goedemans L, Gersh BJ, Holmes DR Jr, Ajmone Marsan N, Delgado V, Bax  
14 JJ. Left Ventricular Post-Infarct Remodeling: Implications for Systolic Function Improvement and  
15 Outcomes in the Modern Era. JACC Heart Fail. 2020;8(2):131-140.  
16  
17 <https://doi.org/10.1016/j.jchf.2019.08.014>  
18
- 19  
20  
21  
22 3 Dorn GW 2nd. Novel pharmacotherapies to abrogate postinfarction ventricular remodeling. Nat Rev  
23 Cardiol 2009;6:283-91. <https://doi.org/10.1038/nrcardio.2009.12>  
24
- 25  
26  
27 4 Symons R, Masci PG, Goetschalckx K, Doulaptsis K, Janssens S, Bogaert J. Effect of infarct  
28 severity on regional and global left ventricular remodeling in patients with successfully reperfused  
29 ST segment elevation myocardial infarction. Radiology. 2015;274:93-102.  
30  
31 <https://doi.org/10.1148/radiol.14132746>  
32
- 33  
34  
35  
36 5 Fertin M, Dubois E, Belliard A, Amouyel P, Pinet F, Bauters C. Usefulness of circulating biomarkers  
37 for the prediction of left ventricular remodeling after myocardial infarction. Am J Cardiol.  
38 2012;110(2):277-83. <https://doi.org/10.1016/j.amjcard.2012.02.069>  
39
- 40  
41  
42  
43 6 Sumiyoshi A, Fujii K, Fukunaga M, Shibuya M, Imanaka T, Kawai K, Miki K, Tamaru H, Horimatsu  
44 T, Saita T, Nishimura M, Masuyama T, Ishihara M. Impact of thermodilution-derived coronary blood  
45 flow patterns after percutaneous coronary intervention on mid-term left ventricular remodeling in  
46 patients with ST elevation myocardial infarction. Heart Vessels. 2017;32(1):1-7.  
47  
48 <https://doi.org/10.1007/s00380-016-0831-0>  
49
- 50  
51  
52  
53  
54 7 Caldentey G, García De Frutos P, Cristóbal H, Garabito M, Berruezo A, Bosch X, San Antonio R,  
55 Flores-Umanzor E, Perea RJ, De Caralt TM, Rodríguez J, Ortiz-Pérez JT. Serum levels of Growth  
56 Arrest-Specific 6 protein and soluble AXL in patients with ST-segment elevation myocardial  
57  
58  
59  
60  
61  
62  
63  
64  
65

- infarction. Eur Heart J Acute Cardiovasc Care. 2019;8(8):708-716.  
<https://doi.org/10.1177/2048872617740833>
- 8 Crilley JG, Farrer M. Left ventricular remodelling and brain natriuretic peptide after first myocardial  
infarction. Heart. 2001;86(6):638-42. <https://doi.org/10.1136/heart.86.6.638>
- 9 Dominguez-Rodriguez A, Abreu-Gonzalez P, Avanzas P. Relation of growth-differentiation factor 15  
to left ventricular remodeling in ST-segment elevation myocardial infarction. Am J Cardiol.  
2011;108(7):955-8. <https://doi.org/10.1016/j.amjcard.2011.05.028>
- 10 Hsu JT, Chung CM, Chu CM, Lin YS, Pan KL, Chang JJ, Wang PC, Chang ST, Yang TY, Jang SJ,  
Yang TH, Hsiao JF. Predictors of Left Ventricle Remodeling: Combined Plasma B-type Natriuretic  
Peptide Decreasing Ratio and Peak Creatine Kinase-MB. Int J Med Sci. 2017;14(1):75-85.  
<https://doi.org/10.7150/ijms.17145>
- 11 Meng L, Wang J, Ding WH, Han P, Yang Y, Qi LT, Zhang BW. Plasma catestatin level in patients  
with acute myocardial infarction and its correlation with ventricular remodelling. Postgrad Med J.  
2013;89(1050):193-6. <https://doi.org/10.1136/postgradmedj-2012-131060>
- 12 Ortiz-Pérez JT, Riera M, Bosch X, De Caralt TM, Perea RJ, Pascual J, Soler MJ. Role of circulating  
angiotensin converting enzyme 2 in left ventricular remodeling following myocardial infarction: a  
prospective controlled study. PLoS One. 2013;8(4):e61695.  
<https://doi.org/10.1371/journal.pone.0061695>
- 13 Yoshitomi Y, Nishikimi T, Kojima S, Kuramochi M, Takishita S, Kangawa K, Matsuo H. Plasma  
natriuretic peptides as indicators of left ventricular remodeling after myocardial infarction. Int J  
Cardiol. 1998;64(2):153-60. [https://doi.org/10.1016/s0167-5273\(98\)00026-6](https://doi.org/10.1016/s0167-5273(98)00026-6)
- 14 Choi H, Yoo BS, Doh JH, Yooh HJ, Ahn MS, Kim JY, Lee SH, Yoon J. The optimal time of B-type  
natriuretic peptide sampling associated with post-myocardial infarction remodelling after primary  
percutaneous coronary intervention. Cardiovasc J Afr. 2013;24(5):165-70.  
<https://doi.org/10.5830/CVJA-2013-024>
- 15 Dominguez-Rodriguez A, Abreu-Gonzalez P, Avanzas P, Laynez-Cerdeña I, Kaski JC. Neopterin  
predicts left ventricular remodeling in patients with ST-segment elevation myocardial infarction

- undergoing primary percutaneous coronary intervention. *Atherosclerosis*. 2010;211(2):574-8.  
<https://doi.org/10.1016/j.atherosclerosis.2010.04.017>
- 16 Gohbara M, Iwahashi N, Kataoka S, Hayakawa Y, Sakamaki K, Akiyama E, Maejima N, Tsukahara K, Hibi K, Kosuge M, Ebina T, Umemura S, Kimura K. Glycemic Variability Determined by Continuous Glucose Monitoring System Predicts Left Ventricular Remodeling in Patients With a First ST-Segment Elevation Myocardial Infarction. *Circ J*. 2015;79(5):1092-9.  
<https://doi.org/10.1253/circj.CJ-14-1226>
- 17 Swiatkiewicz I, Kozinski M, Magielski P, Fabiszak T, Sukiennik A, Navarese EP, Odrowaz-Sypniewska G, Kubica J. Value of C-reactive protein in predicting left ventricular remodelling in patients with a first ST-segment elevation myocardial infarction. *Mediators Inflamm*. 2012;2012:250867. <https://doi.org/10.1155/2012/250867>
- 18 Cerisano G, Pucci PD, Sulla A, Tommasi M, Raspanti S, Santoro GM, Antoniucci D. Relation between plasma brain natriuretic peptide, serum indexes of collagen type I turnover, and left ventricular remodeling after reperfused acute myocardial infarction. *Am J Cardiol*. 2007;99(5):651-6. <https://doi.org/10.1016/j.amjcard.2006.09.114>
- 19 Fertin M, Hennache B, Hamon M, Ennezat PV, Biaisque F, Elkohen M, Nague O, Tricot O, Lamblin N, Pinet F, Bauters C. Usefulness of serial assessment of B-type natriuretic peptide, troponin I, and C-reactive protein to predict left ventricular remodeling after acute myocardial infarction (from the REVE-2 study). *Am J Cardiol*. 2010;106(10):1410-6. <https://doi.org/10.1016/j.amjcard.2010.06.071>
- 20 Garcia-Alvarez A, Sitges M, Delgado V, Ortiz J, Vidal B, Poyatos S, de Caralt TM, Heras M, Bosch X, Azqueta M, Pare C, Brugada J. Relation of plasma brain natriuretic peptide levels on admission for ST-elevation myocardial infarction to left ventricular end-diastolic volume six months later measured by both echocardiography and cardiac magnetic resonance. *Am J Cardiol*. 2009;104(7):878-82. <https://doi.org/10.1016/j.amjcard.2009.05.025>
- 21 Türkoğlu C, Gür M, Şeker T, Selek Ş, Koçyiğit A. The predictive value of M30 and oxidative stress for left ventricular remodeling in patients with anterior ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *Coron Artery Dis*. 2016;27(8):690-695.  
<https://doi.org/10.1097/MCA.0000000000000416>

- 22 Sato A, Aonuma K, Imanaka-Yoshida K, Yoshida T, Isobe M, Kawase D, Kinoshita N, Yazaki Y, Hiroe M. Serum tenascin-C might be a novel predictor of left ventricular remodeling and prognosis after acute myocardial infarction. *J Am Coll Cardiol.* 2006;47(11):2319-25. <https://doi.org/10.1016/j.jacc.2006.03.033>
- 23 Bauters A, Fertin M, Lamblin N, Pinet F, Bauters C. White blood cell and peripheral blood mononuclear cell counts for the prediction of left ventricular remodeling after myocardial infarction. *J Cardiol.* 2011;58(2):197-8. <https://doi.org/10.1016/j.jjcc.2011.06.002>
- 24 Wu W, Li J, Yu C, Gao Y, Fan S, Ye X, Wang Y, Zheng J. Association of serum ADAMTS-7 levels with left ventricular reverse remodeling after ST-elevation myocardial infarction. *Eur J Med Res.* 2018;23(1):15. <https://doi.org/10.1186/s40001-018-0305-1>
- 25 Hsiao JF, Chung CM, Chu CM, Lin YS, Pan KL, Chang ST, Hsu JT. Two-Dimensional Speckle Tracking Echocardiography Predict Left Ventricular Remodeling after Acute Myocardial Infarction in Patients with Preserved Ejection Fraction. *PLoS One.* 2016;11(12):e0168109. <https://doi.org/10.1371/journal.pone.0168109>
- 26 López Haldón J, Fernández Quero M, Mancha F, Urbano JA, Guisado A, Villa M, Valle JI, Rodríguez Puras MJ, Ballesteros S, López Pardo F, Díaz de la Llera L, Sánchez González A, Martínez Martínez A. Value of NT-ProBNP level and echocardiographic parameters in ST-segment elevation myocardial infarction treated by primary angioplasty: relationships between these variables and their usefulness as predictors of ventricular remodeling. *Rev Esp Cardiol.* 2010;63(9):1019-27. [https://doi.org/10.1016/s1885-5857\(10\)70205-x](https://doi.org/10.1016/s1885-5857(10)70205-x)
- 27 Garcia G, Chao de la Barca JM, Mirebeau-Prunier D, Reynier P, Furber A, Prunier F, Bière L. Metabolomic Approach in STEMI-Patients Undergoing Left Ventricular Remodeling. *Int J Mol Sci.* 2019;20(2):289. <https://doi.org/10.3390/ijms20020289>
- 28 Na HM, Cho GY, Lee JM, Cha MJ, Yoon YE, Lee SP, Kim HK, Kim YJ, Sohn DW. Echocardiographic Predictors for Left Ventricular Remodeling after Acute ST Elevation Myocardial Infarction with Low Risk Group: Speckle Tracking Analysis. *J Cardiovasc Ultrasound.* 2016;24(2):128-34. <https://doi.org/10.4250/jcu.2016.24.2.128>

- 29 Di Tano G, Caretta G, De Maria R, Parolini M, Bassi L, Testa S, Pirelli S. Galectin-3 predicts left ventricular remodelling after anterior-wall myocardial infarction treated by primary percutaneous coronary intervention. *Heart*. 2017;103(1):71-77. <https://doi.org/10.1136/heartjnl-2016-309673>
- 30 Liu X, Dong Y, Chen S, Zhang G, Zhang M, Gong Y, Li X. Circulating MicroRNA-146a and MicroRNA-21 Predict Left Ventricular Remodeling after ST-Elevation Myocardial Infarction. *Cardiology*. 2015;132(4):233-41. <https://doi.org/10.1159/000437090>
- 31 Urbano-Moral JA, Lopez-Haldon JE, Fernandez M, Mancha F, Sanchez A, Rodriguez-Puras MJ, Villa M, Lopez-Pardo F, Diaz de la Llera L, Valle JI, Martinez A. Prognostic value of different serum biomarkers for left ventricular remodelling after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. 2012;98(15):1153-9. <https://doi.org/10.1136/heartjnl-2012-301636>
- 32 Giallauria F, Cirillo P, Lucci R, Pacileo M, De Lorenzo A, D'Agostino M, Moschella S, Psaroudaki M, Del Forno D, Orio F, Vitale DF, Chiariello M, Vigorito C. Left ventricular remodelling in patients with moderate systolic dysfunction after myocardial infarction: favourable effects of exercise training and predictive role of N-terminal pro-brain natriuretic peptide. *Eur J Cardiovasc Prev Rehabil*. 2008;15(1):113-8. <https://doi.org/10.1097/HJR.0b013e3282f00990>
- 33 Kercheva M, Ryabova T, Gusakova A, Suslova TE, Ryabov V, Karpov RS. Serum Soluble ST2 and Adverse Left Ventricular Remodeling in Patients With ST-Segment Elevation Myocardial Infarction. *Clin Med Insights Cardiol*. 2019;13:1179546819842804
- 34 Reindl M, Reinstadler SJ, Feistritz HJ, Mueller L, Koch C, Mayr A, Theurl M, Kirchmair R, Klug G, Metzler B. Fibroblast growth factor 23 as novel biomarker for early risk stratification after ST-elevation myocardial infarction. *Heart*. 2017;103(11):856-862. <https://doi.org/10.1136/heartjnl-2016-310520>
- 35 Devaux Y, Vausort M, McCann GP, Zangrando J, Kelly D, Razvi N, Zhang L, Ng LL, Wagner DR, Squire IB. MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. *Circ Cardiovasc Genet*. 2013;6(3):290-8. <https://doi.org/10.1161/CIRCGENETICS.113.000077>

- 36 Lv P, Zhou M, He J, Meng W, Ma X, Dong S, Meng X, Zhao X, Wang X, He F. Circulating miR-208b and miR-34a are associated with left ventricular remodeling after acute myocardial infarction. *Int J Mol Sci.* 2014;15(4):5774-88. <https://doi.org/10.3390/ijms15045774>
- 37 Reinstadler SJ, Feistritzer HJ, Reindl M, Klug G, Mayr A, Mair J, Jaschke W, Metzler B. Combined biomarker testing for the prediction of left ventricular remodelling in ST-elevation myocardial infarction. *Open Heart.* 2016;3(2):e000485. <https://doi.org/10.1136/openhrt-2016-000485>
- 38 Xiaozhou H, Jie Z, Li Z, Liyan C. Predictive value of the serum level of N-terminal pro-brain natriuretic peptide and high-sensitivity C-reactive protein in left ventricular remodeling after acute myocardial infarction. *J Clin Lab Anal.* 2006;20(1):19-22. <https://doi.org/10.1002/jcla.20094>
- 39 Kelly D, Khan SQ, Thompson M, Cockerill G, Ng LL, Samani N, Squire IB. Plasma tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9: novel indicators of left ventricular remodelling and prognosis after acute myocardial infarction. *Eur Heart J.* 2008;29(17):2116-24. <https://doi.org/10.1093/eurheartj/ehn315>
- 40 Bière L, Garcia G, Guillo S, Larcher F, Furber A, Willoteaux S, Mirebeau-Prunier D, Prunier F. ST2 as a predictor of late ventricular remodeling after myocardial infarction. *Int J Cardiol.* 2018;259:40-42. <https://doi.org/10.1016/j.ijcard.2018.02.058>
- 41 Kelly D, Cockerill G, Ng LL, Thompson M, Khan S, Samani NJ, Squire IB. Plasma matrix metalloproteinase-9 and left ventricular remodelling after acute myocardial infarction in man: a prospective cohort study. *Eur Heart J.* 2007;28(6):711-8. <https://doi.org/10.1093/eurheartj/ehm003>
- 42 Manhenke C, Ueland T, Jugdutt BI, Godang K, Aukrust P, Dickstein K, Ørn S. The relationship between markers of extracellular cardiac matrix turnover: infarct healing and left ventricular remodelling following primary PCI in patients with first-time STEMI. *Eur Heart J.* 2014;35(6):395-402. <https://doi.org/10.1093/eurheartj/eh482>
- 43 Mather AN, Fairbairn TA, Artis NJ, Greenwood JP, Plein S. Relationship of cardiac biomarkers and reversible and irreversible myocardial injury following acute myocardial infarction as determined by cardiovascular magnetic resonance. *Int J Cardiol.* 2013;166(2):458-64. <https://doi.org/10.1016/j.ijcard.2011.11.004>

- 44 Reinstadler SJ, Klug G, Feistritz HJ, Mayr A, Harrasser B, Mair J, Bader K, Streil K, Hammerer-Lercher A, Esterhammer R, Metzler B. Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. *Heart*. 2013;99(20):1525-9. <https://doi.org/10.1136/heartjnl-2013-303975>
- 45 Feistritz HJ, Klug G, Reinstadler SJ, Gröber MT, Mair J, Kirchmair R, Henninger B, Franz WM, Metzler B. Fetuin-A is related to infarct size, left ventricular function and remodelling after acute STEMI. *Open Heart*. 2015;2(1):e000244. <https://doi.org/10.1136/openhrt-2015-000244>
- 46 Kim EK, Song YB, Chang SA, Park SJ, Hahn JY, Choi SH, Choi JH, Gwon HC, Park SW, Choe YH, Ahn J, Carriere K, Lee SC. Is cardiac magnetic resonance necessary for prediction of left ventricular remodeling in patients with reperfused ST-segment elevation myocardial infarction? *Int J Cardiovasc Imaging*. 2017;33(12):2003-2012. <https://doi.org/10.1007/s10554-017-1206-z>
- 47 Lin JF, Hsu SY, Wu S, Teng MS, Chou HH, Cheng ST, Wu TY, Ko YL. QT interval Independently Predicts Mortality and Heart Failure in Patients with ST-Elevation Myocardial Infarction. *Int J Med Sci*. 2015;12(12):968-73. <https://doi.org/10.7150/ijms.13121>
- 48 Liu PY, Chen CL, Yu MC, Ko YL, Hsu SY, Chou HH, Yeh KH, Duan DM, Chen MH, Lin JF. Doses of renin-angiotensin system inhibitors but not beta-blockers predict outcome after ST-elevation myocardial infarction. *Acta Clin Belg*. 2019;74(5):334-341. <https://doi.org/10.1080/17843286.2018.1528708>
- 49 Nilsson JC, Groenning BA, Nielsen G, Fritz-Hansen T, Trawinski J, Hildebrandt PR, Jensen GB, Larsson HB, Sondergaard L. Left ventricular remodeling in the first year after acute myocardial infarction and the predictive value of N-terminal pro brain natriuretic peptide. *Am Heart J*. 2002;143(4):696-702. <https://doi.org/10.1067/mhj.2002.120293>
- 50 Khurelsukh K, Kim YH, Seon HJ, Song JH, Park SY, Moon SM, Kim SH, Sim DS, Ahn Y. Non-contrast cardiac CT immediately after percutaneous coronary intervention: does it predict the risk of left ventricular remodeling in patients with ST-elevation myocardial infarction? *Int J Cardiovasc Imaging*. 2016;32 Suppl 1:147-54. <https://doi.org/10.1007/s10554-016-0900-6>
- 51 Andrejic OM, Vucic RM, Pavlovic M, McClements L, Stokanovic D, Jevtovic-Stoimenov T, Nikolic VN. Association between Galectin-3 levels within central and peripheral venous blood, and adverse

- left ventricular remodelling after first acute myocardial infarction. *Sci Rep.* 2019;9(1):13145.  
<https://doi.org/10.1038/s41598-019-49511-4>
- 52 Barberato SH, Souza AM, Costantini CO, Costantini CR. Non invasive assessment of left ventricular filling pressure and remodeling after acute myocardial infarction. *Arq Bras Cardiol.* 2013;100(6):531-7. <https://doi.org/10.5935/abc.20130092>
- 53 Abdel Hamid M, Bakhoun SW, Sharaf Y, Sabry D, El-Gengehe AT, Abdel-Latif A. Circulating Endothelial Cells and Endothelial Function Predict Major Adverse Cardiac Events and Early Adverse Left Ventricular Remodeling in Patients With ST-Segment Elevation Myocardial Infarction. *J Interv Cardiol.* 2016;29(1):89-98. <https://doi.org/10.1111/joic.12269>
- 54 Bonios MJ, Kaladaridou A, Tasoulis A, Papadopoulou E, Pamboukas C, Ntalianis A, Kanakakis J, Terrovitis JV, Toumanidis ST. Value of apical circumferential strain in the early post-myocardial infarction period for prediction of left ventricular remodeling. *Hellenic J Cardiol.* 2014;55(4):305-12.
- 55 Caldentey G, García De Frutos P, Cristóbal H, Garabito M, Berrueto A, Bosch X, San Antonio R, Flores-Umanzor E, Perea RJ, De Caralt TM, Rodríguez J, Ortiz-Pérez JT. Serum levels of Growth Arrest-Specific 6 protein and soluble AXL in patients with ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care.* 2019;8(8):708-716
- 56 Bochenek T, Wita K, Tabor Z, Grabka M, Krzych Ł, Wróbel W, Berger-Kucza A, Elżbieciak M, Doruchowska A, Gluza MT. Value of speckle-tracking echocardiography for prediction of left ventricular remodeling in patients with ST-elevation myocardial infarction treated by primary percutaneous intervention. *J Am Soc Echocardiogr.* 2011;24(12):1342-8. <https://doi.org/10.1016/j.echo.2011.09.003>
- 57 Aoki S, Nakagomi A, Asai K, Takano H, Yasutake M, Seino Y, Mizuno K. Elevated peripheral blood mononuclear cell count is an independent predictor of left ventricular remodeling in patients with acute myocardial infarction. *J Cardiol.* 2011;57(2):202-7. <https://doi.org/10.1016/j.jjcc.2010.10.003>
- 58 Zaliaduonyte-Peksiene D, Simonyte S, Lesauskaite V, Vaskelyte J, Gustiene O, Mizariene V, Jurkevicius R, Jariene G, Tamosiunas A, Zaliunas R. Left ventricular remodelling after acute myocardial infarction: impact of clinical, echocardiographic parameters and polymorphism of

- angiotensinogen gene. *J Renin Angiotensin Aldosterone Syst.* 2014;15(3):286-93.  
<https://doi.org/10.1177/1470320312471228>
- 59 Karuzas A, Rumbinaite E, Verikas D, Ptasinikas T, Muckiene G, Kazakauskaite E, Zabiela V,  
Jurkevicius R, Vaskelyte JJ, Zaliunas R, Zaliaduonyte-Peksiene D. Accuracy of three-dimensional  
systolic dyssynchrony and sphericity indexes for identifying early left ventricular remodeling after  
acute myocardial infarction. *Anatol J Cardiol.* 2019;22(1):13-20.  
<https://doi.org/10.14744/AnatolJCardiol.2019.02844>
- 60 Buono F, Spinelli L, Giallauria F, Assante di Panzillo E, Di Marino S, Ferrara F, Vigorito C,  
Trimarco B, Morisco C. Usefulness of satisfactory control of low-density lipoprotein cholesterol to  
predict left ventricular remodeling after a first ST-elevation myocardial infarction successfully  
reperfused. *Am J Cardiol.* 2011;107(12):1772-8. <https://doi.org/10.1016/j.amjcard.2011.01.066>
- 61 Reindl M, Reinstadler SJ, Feistritzer HJ, Tiller C, Mayr A, Klug G, Metzler B. Heart rate and left  
ventricular adverse remodelling after ST-elevation myocardial infarction. *Int J Cardiol.*  
2016;219:339-44. <https://doi.org/10.1016/j.ijcard.2016.06.046>
- 62 Joyce E, Hoogslag GE, Leong DP, Fox K, Schali J, Marsan NA, Bax JJ, Delgado V. Association  
between discharge heart rate and left ventricular adverse remodelling in ST segment elevation  
myocardial infarction patients treated with primary percutaneous coronary intervention. *Heart.*  
2013;99(8):556-61. <https://doi.org/10.1136/heartjnl-2012-303406>
- 63 Piestrzeniewicz K, Luczak K, Maciejewski M, Drozd J. Low adiponectin blood concentration  
predicts left ventricular remodeling after ST-segment elevation myocardial infarction treated with  
primary percutaneous coronary intervention. *Cardiol J.* 2010;17(1):49-56.
- 64 Bauters C, Ennezat PV, Tricot O, Lauwerier B, Lallemand R, Saadouni H, Quandalle P, Jaboureck O,  
Lamblin N, Le Tourneau T; REVE Investigators. Stress hyperglycaemia is an independent predictor  
of left ventricular remodelling after first anterior myocardial infarction in non-diabetic patients. *Eur*  
*Heart J.* 2007;28(5):546-52. <https://doi.org/10.1093/eurheartj/ehl546>
- 65 Nicolau JC, Maia LN, Vitola JV, Mahaffey KW, Machado MN, Ramires JA. Baseline glucose and  
left ventricular remodeling after acute myocardial infarction. *J Diabetes Complications.*  
2007;21(5):294-9. <https://doi.org/10.1016/j.jdiacomp.2006.01.003>

- 66 Schoos MM, Munthe-Fog L, Skjoedt MO, Ripa RS, Lønborg J, Kastrup J, Kelbæk H, Clemmensen P, Garred P. Association between lectin complement pathway initiators, C-reactive protein and left ventricular remodeling in myocardial infarction-a magnetic resonance study. *Mol Immunol*. 2013;54(3-4):408-14. <https://doi.org/10.1016/j.molimm.2013.01.008>
- 67 Reindl M, Feistritzer HJ, Reinstadler SJ, Mueller L, Tiller C, Brenner C, Mayr A, Henninger B, Mair J, Klug G, Metzler B. Thyroid-stimulating hormone and adverse left ventricular remodeling following ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2019;8(8):717-726. <https://doi.org/10.1177/2048872618770600>
- 68 Choe JC, Cha KS, Yun EY, Ahn J, Park JS, Lee HW, Oh JH, Kim JS, Choi JH, Park YH, Lee HC, Kim JH, Chun KJ, Hong TJ, Ahn Y, Jeong MH, Chae SC, Kim YJ; Korea Acute Myocardial Infarction Registry Investigators. Reverse Left Ventricular Remodelling in ST-Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention: Incidence, Predictors, and Impact on Outcome. *Heart Lung Circ*. 2018;27(2):154-164. <https://doi.org/10.1016/j.hlc.2017.02.020>
- 69 Fertin M, Lemesle G, Turkieh A, Beseme O, Chwastyniak M, Amouyel P, Bauters C, Pinet F. Serum MMP-8: a novel indicator of left ventricular remodeling and cardiac outcome in patients after acute myocardial infarction. *PLoS One*. 2013;8(8):e71280. <https://doi.org/10.1371/journal.pone.0071280>
- 70 Cerisano G, Buonamici P, Gori AM, Valenti R, Sciagrà R, Giusti B, Sereni A, Raspanti S, Colonna P, Gensini GF, Abbate R, Schulz R, Antonucci D. Matrix metalloproteinases and their tissue inhibitor after reperfused ST-elevation myocardial infarction treated with doxycycline. Insights from the TIPTOP trial. *Int J Cardiol*. 2015;197:147-53. <https://doi.org/10.1016/j.ijcard.2015.06.024>
- 71 Nilsson L, Hallén J, Atar D, Jonasson L, Swahn E. Early measurements of plasma matrix metalloproteinase-2 predict infarct size and ventricular dysfunction in ST-elevation myocardial infarction. *Heart*. 2012;98(1):31-6. <https://doi.org/10.1136/heartjnl-2011-300079>
- 72 Webb CS, Bonnema DD, Ahmed SH, Leonardi AH, McClure CD, Clark LL, Stroud RE, Corn WC, Finklea L, Zile MR, Spinale FG. Specific temporal profile of matrix metalloproteinase release occurs in patients after myocardial infarction: relation to left ventricular remodeling. *Circulation*. 2006;114(10):1020-7. <https://doi.org/10.1161/CIRCULATIONAHA.105.600353>

- 73 Kelly D, Khan S, Cockerill G, Ng LL, Thompson M, Samani NJ, Squire IB. Circulating stromelysin-1 (MMP-3): a novel predictor of LV dysfunction, remodelling and all-cause mortality after acute myocardial infarction. *Eur J Heart Fail.* 2008;10(2):133-9. <https://doi.org/10.1016/j.ejheart.2007.12.009>
- 74 Radovan J, Vaclav P, Petr W, Jan C, Michal A, Richard P, Martina P. Changes of collagen metabolism predict the left ventricular remodeling after myocardial infarction. *Mol Cell Biochem.* 2006;293(1-2):71-8. <https://doi.org/10.1007/s11010-006-2955-5>
- 75 Poulsen SH, Høst NB, Jensen SE, Egstrup K. Relationship between serum amino-terminal propeptide of type III procollagen and changes of left ventricular function after acute myocardial infarction. *Circulation.* 2000;101(13):1527-32. <https://doi.org/10.1161/01.cir.101.13.1527>
- 76 Lamblin N, Bauters A, Fertin M, de Groote P, Pinet F, Bauters C. Circulating levels of hepatocyte growth factor and left ventricular remodelling after acute myocardial infarction (from the REVE-2 study). *Eur J Heart Fail.* 2011;13(12):1314-22. <https://doi.org/10.1093/eurjhf/hfr137>
- 77 Soeki T, Tamura Y, Shinohara H, Sakabe K, Onose Y, Fukuda N. Serum hepatocyte growth factor predicts ventricular remodeling following myocardial infarction. *Circ J.* 2002;66(11):1003-7. <https://doi.org/10.1253/circj.66.1003>
- 78 Stamboul K, Zeller M, Rochette L, Cottin Y, Cochet A, Leclercq T, Porot G, Guenancia C, Fichot M, Maillot N, Vergely C, Lorgis L. Relation between high levels of myeloperoxidase in the culprit artery and microvascular obstruction, infarct size and reverse remodeling in ST-elevation myocardial infarction. *PLoS One.* 2017;12(7):e0179929. <https://doi.org/10.1371/journal.pone.0179929>
- 79 Yunoki K, Naruko T, Komatsu R, Shirai N, Nakagawa M, Sugioka K, Ikura Y, Kusano KF, Itoh A, Haze K, Yoshiyama M, Becker AE, Ueda M. Relation of elevated levels of plasma myeloperoxidase to impaired myocardial microcirculation after reperfusion in patients with acute myocardial infarction. *Am J Cardiol.* 2010;105(7):922-9. <https://doi.org/10.1016/j.amjcard.2009.11.013>
- 80 Erkol A, Oduncu V, Pala S, Kızıllırmak F, Kılıçgedik A, Yılmaz F, Güler A, Karabay CY, Kırmacı C. Plasma osteoprotegerin level on admission is associated with no-reflow phenomenon after primary angioplasty and subsequent left ventricular remodeling in patients with acute ST-segment elevation

- myocardial infarction. *Atherosclerosis*. 2012;221(1):254-9.  
<https://doi.org/10.1016/j.atherosclerosis.2011.12.031>
- 81 Shetelig C, Limalanathan S, Eritsland J, Hoffmann P, Seljeflot I, Gran JM, Aukrust P, Ueland T, Andersen GØ. Osteoprotegerin levels in ST-elevation myocardial infarction: Temporal profile and association with myocardial injury and left ventricular function. *PLoS One*. 2017;12(3):e0173034.  
<https://doi.org/10.1371/journal.pone.0173034>
- 82 Dominguez-Rodriguez A, Abreu-Gonzalez P, Arroyo-Ucar E, Reiter RJ. Decreased level of melatonin in serum predicts left ventricular remodelling after acute myocardial infarction. *J Pineal Res*. 2012;53(3):319-23. <https://doi.org/10.1111/j.1600-079X.2012.01001.x>
- 83 Devaux Y, Vausort M, Azuaje F, Vaillant M, Lair ML, Gayat E, Lassus J, Ng LL, Kelly D, Wagner DR, Squire IB. Low levels of vascular endothelial growth factor B predict left ventricular remodeling after acute myocardial infarction. *J Card Fail*. 2012;18(4):330-7.  
<https://doi.org/10.1016/j.cardfail.2012.01.010>
- 84 Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177.  
<https://doi.org/10.1093/eurheartj/ehx393>
- 85 Jugdutt BI. Pleiotropic effects of cardiac drugs on healing post-MI. The good, bad, and ugly. *Heart Fail Rev*. 2008;13(4):439-52. <https://doi.org/10.1007/s10741-008-9090-1>
- 86 Anavekar NS, Solomon SD. Angiotensin II receptor blockade and ventricular remodelling. *J Renin Angiotensin Aldosterone Syst*. 2005;6(1):43-8. <https://doi.org/10.3317/jraas.2005.006>
- 87 Prabhu SD, Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis. *Circ Res*. 2016;119(1):91-112.  
<https://doi.org/10.1161/CIRCRESAHA.116.303577>

- 88 Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. *Circulation Research* 2012;110(1):159–173. <https://doi.org/10.1161/CIRCRESAHA.116.303577>
- 89 Bujak M, Frangogiannis NG. The role of TGF-beta signaling in myocardial infarction and cardiac remodeling. *Cardiovasc Res*. 2007;74(2):184-95. <https://doi.org/10.1016/j.cardiores.2006.10.002>
- 90 Legallois D, Hodzic A, Alexandre J, Dolladille C, Saloux E, Manrique A, Roule V, Labombarda F, Milliez P, Beygui F. Definition of left ventricular remodelling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade. *Heart Fail Rev*. 2020. <https://doi.org/10.1007/s10741-020-09975-3>
- 91 Kelly D, Squire IB, Khan SQ, Quinn P, Struck J, Morgenthaler NG, Davies JE, Ng LL. C-terminal pro-vasopressin (copeptin) is associated with left ventricular dysfunction, remodeling, and clinical heart failure in survivors of myocardial infarction. *J Card Fail*. 2008;14(9):739-45. <https://doi.org/10.1016/j.cardfail.2008.07.231>

**FIGURE LEGENDS**

**Figure 1.** Evolution of biomarkers levels after STEMI in case of small infarct area (lower panel) and large infarct area (upper panel). A larger infarcted myocardium leads to a higher level of biomarkers of myocardial damage and enhanced inflammation, activation of neurohormonal activation and matrix turnover and then, adverse left ventricular remodeling. LV: left ventricular, STEMI: ST-elevation myocardial infarction.

## TABLES

**Table 1.** Association between natriuretic peptides levels and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; BNP, brain natriuretic peptide ; CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV(i), (indexed) end-systolic volume ; LVR, left ventricular remodeling ; MI, myocardial infarction ; PCI, percutaneous coronary intervention ; SPECT, single positron emission computed tomography ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

**Table 2.** Association between complete blood test data and LVR at follow-up in STEMI patients. CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV, end-systolic volume ; LVR, left ventricular remodeling ; MI, myocardial infarction ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

**Table 3.** Association between glucose levels and LVR at follow-up in STEMI patients. CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV, end-systolic volume ; LVR, left ventricular remodeling ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

**Table 4.** Association between biomarkers of inflammation and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; CMR, cardiac magnetic resonance ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

**Table 5.** Association between biomarkers involved in the turnover of matrix and collagen synthesis and degradation and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV(i), (indexed) end-systolic volume ; LVR, left ventricular remodeling ; MI, myocardial infarction ; MMP, matrix metalloproteinase ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TIMP, tissue inhibitor of metalloproteinase ; TTE, transthoracic echocardiography.

**Table 6.** Association between remaining circulating biomarkers not included in previous tables and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV(i), (indexed) end-systolic volume ; LVG, left ventriculography ; LVR, left ventricular remodeling ; MI, myocardial infarction ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

Table 1

|                                                                                                   | sample size        | biomarker assessment                                        | follow-up imaging | definition of LVR                                               | LVR                   | correlation                                   | relationship                                                                                                                                                   | comments                                  |
|---------------------------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------|-------------------|-----------------------------------------------------------------|-----------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>BNP</b>                                                                                        |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+</i> |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| Caldeney et al. (7)                                                                               | 227                | 48 hours after admission                                    | CMR, 6 mo         | $\Delta\text{EDV} \geq 20\%$                                    | 29 (16%)              | none                                          | 140±107 vs. 146±114 ; p=0.859                                                                                                                                  | pg/mL                                     |
| Crilly et al. (8)                                                                                 | 126                | day 3 to 7                                                  | TTE, 2 mo         | $\Delta\text{ESV} \geq 10\%$                                    | 45 (36%)              | positive                                      | p=0.034                                                                                                                                                        |                                           |
| Dominguez-Rodriguez et al. (9)                                                                    | 97                 | at admission                                                | TTE, 12 mo        | $\Delta\text{EDV} > 20\%$                                       | 21 (21.6%)            | none                                          | 450 (421-485) vs. 473 (406-415) ; p=0.18                                                                                                                       | pg/mL                                     |
| Hsu et al. (10)                                                                                   | 97<br>(61 % STEMl) | day 2, day 7                                                | TTE, 6 mo         | $\Delta\text{EDV} > 20\%$                                       | 24 (32.9%)            | none                                          | 322.0±440.2 vs. 342.1±369.5 ; p=0.841                                                                                                                          | pg/mL, day 2                              |
| Meng et al. (11)                                                                                  | 31<br>(67 % STEMl) | at admission, day 3 and day 7                               | TTE, 3 mo         | $\Delta\text{EDV} > 20\%$                                       | 7 (22.6%)             | none                                          | 224.7±305.7 vs. 327.8±256.1 ; p=0.148                                                                                                                          | pg/mL, day 7                              |
| Ortiz-Perez et al. (12)                                                                           | 88                 | 48 hours                                                    | CMR, 6.4 mo       | $\Delta\text{EDV} \geq 20\%$                                    | 15 (16.9%)            | none                                          | 135.8 (13.0 - 725.6) vs. 255 (14.0-2378) ; p=0.277                                                                                                             | admission                                 |
| Yoshitomi et al. (13)                                                                             | 33                 | at admission                                                | LVG, 3 mo         | $\Delta\text{EDV} \geq 8\%$                                     | 14 (42.4%)            | positive                                      | 121.1 (26.6-585.8) vs. 935 (51.9-2287) ; p=0.033                                                                                                               | day 7                                     |
| <i>logistic regression</i>                                                                        |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| Choi et al. (14)                                                                                  | 131                | at admission, day 2 to 5                                    | TTE, 6 mo         | $\Delta\text{EDV} > 20\%$                                       | 42 (32%)              | variable, multivariate positive, multivariate | OR range : 1.005-1.008 ; p range 0.01-0.08<br>OR range : 1.011-1.013 ; p<0.01 (all models)                                                                     | pg/mL<br>on admission<br>day 2 to 5       |
| Dominguez-Rodriguez et al. (15)                                                                   | 108                | before primary PCI                                          | TTE, 12 mo        | $\Delta\text{EDV} > 20\%$                                       | 21 (19%)              | none                                          | OR 1.006, 95%CI [0.999, 1.013] ; p=0.07                                                                                                                        |                                           |
| Gobbara et al. (16)                                                                               | 69                 | at admission, 6 hours, daily until discharge                | CMR, 7 mo         | $\Delta\text{EDV} \geq 20\%$                                    | 18 (26.1%)            | negative                                      | OR 0.977, 95%CI [0.955, 0.999] ; p=0.045                                                                                                                       | per 1 pg/mL                               |
| Swiatkiewicz et al. (17)                                                                          | 198                | at admission, discharge                                     | TTE, 6 mo         | $\Delta\text{EDV} > 20\%$                                       | 55 (27.8%)            | none<br>positive<br>positive, multivariate    | OR 0.978, 95%CI [0.951, 1.007] ; p=0.136<br>OR 1.08, 95%CI [0.88, 1.33] ; p=NS<br>OR 1.14, 95%CI [1.02, 1.28] ; p<0.05<br>OR 1.21, 95%CI [1.05, 1.39] ; p<0.01 | admission,<br>discharge,<br>per 100 pg/mL |
| <i>linear regression</i>                                                                          |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| Cerisano et al. (18)                                                                              | 56                 | day 1, day 3                                                | TTE, 6 mo         | $\Delta\text{LVEDVI} > 2$<br>times the SD of<br>baseline values | 17 (30%)              | positive                                      | beta coefficient 1.001, 95%CI [1.001, 1.007] ; p=0.02<br>beta coefficient 0.992, 95%CI [0.983, 1.000] ; p=0.06                                                 |                                           |
| Fertin et al. (19)                                                                                | 226<br>(Q-wave MI) | at discharge (day 3 to day 7)                               | TTE, 12 mo        | $\Delta\text{EDV} > 20\%$                                       | 87 (38%)              | positive (all time points)                    | beta coefficient 0.207 ; p=0.002                                                                                                                               |                                           |
| Garcia-Alvarez et al. (20)                                                                        | 78                 | within the first 24 to 96 hours after the onset of symptoms | TTE and CMR, 6 mo | $\Delta\text{EDV} > 20\%$                                       | 26 (31.7%)            | positive                                      | B coefficient 0.07, 95%CI [0.01, 0.13] ; p=0.01<br>B coefficient 0.08, 95%CI [0.01, 0.15] ; p=0.04                                                             | pg/mL                                     |
| Turkoğlu et al. (21)                                                                              | 255                | at admission, 24 hours                                      | TTE, 6 mo         | $\Delta\text{EDV} \geq 20\%$                                    | 60 (23.5%)            | positive, multivariate                        | beta coefficient 4.996, 95%CI [2.703, 9.232] ; p<0.001                                                                                                         |                                           |
| <i>ROC curve</i>                                                                                  |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| Sato et al. (22)                                                                                  | 105                | day 5                                                       | SPECT, 44 mo      | $\Delta\text{EDV} \geq 20\%$                                    | 25 (23.8%)            | positive                                      | AUC 0.817, cut-off value 138 pg/mL,<br>sensitivity 92 %, specificity 71 %                                                                                      | day 5                                     |
| <i>not described</i>                                                                              |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| Bauters et al. (23)                                                                               | 226<br>(Q-wave MI) | at admission                                                | TTE, 12 mo        | percent change in<br>LVEDV                                      | NA                    | positive, multivariate                        |                                                                                                                                                                |                                           |
| <b>Peak BNP</b>                                                                                   |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| Wu et al. (24)                                                                                    | 104                | day 1, day 3, day 5 and day 7                               | TTE, 6 months     | $\geq 15\%$ decrease in<br>LVESV (reverse<br>remodeling)        | 56 (53.8%)<br>reverse | none                                          | 223.7±213.5 vs. 188.4±129.8 ; p=0.35                                                                                                                           | pg/mL                                     |
| <b>log BNP</b>                                                                                    |                    |                                                             |                   |                                                                 |                       |                                               |                                                                                                                                                                |                                           |
| Hsiao et al. (25)                                                                                 | 54                 | immediately, 8 hours, 16 hours                              | TTE, 6 mo         | $\Delta\text{ESV} > 15\%$                                       | 19 (35.2%)            | positive                                      | OR 2.89, 95%CI [1.06, 7.88] ; p=0.04                                                                                                                           | log ng/L                                  |

| <b>NT-proBNP</b>                                                                                  |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
|---------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------|----------------------------------------------------|-------------------------|-------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------|--|
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+</i> |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
| López Haldón et al. (26)                                                                          | 159                                              | before PCI and discharge                                 | TTE, 6 mo                                          | ΔEDV≥20 %               | 31 (19.5%)  | none                                 | 374±799 vs. 460±941 ; p=0.66                                                                                             | pg/mL, admission            |  |
| García et al. (27)                                                                                | 64                                               | 48h [IQR 24-72]                                          | CMR, 3/12 mo                                       | ΔESV>10%                | NA          | positive                             | 945±1630 vs. 1957±2000 ; p=0.016                                                                                         | pg/mL, discharge            |  |
| Na et al. (28)                                                                                    | 208                                              | unavailable                                              | TTE, 6 mo                                          | ΔEDV>20%                | 53 (25.5%)  | none                                 | 1375±1630 vs. 1844±1882 ; p=0.23                                                                                         | ng/L                        |  |
| <i>logistic regression</i>                                                                        |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
| Di Tano et al. (29)                                                                               | 92                                               | baseline                                                 | TTE, 6 mo                                          | ΔESV≥15 %               | 26 (28.2%)  | positive                             | 594±1312 vs. 525±1217 ; p=0.759                                                                                          | pg/mL                       |  |
| Liu et al. (30)                                                                                   | 198                                              | day 5                                                    | TTE, 12 mo                                         | ΔEDV≥20 %               | 56 (28.3%)  | none, multivariate                   | OR 1.15, 95%CI [1.04, 1.27] ; p=0.007                                                                                    | per 1000 ng/mL              |  |
| Urbano-Moral et al. (31)                                                                          | 112                                              | during PCI and discharge                                 | TTE, 6 mo                                          | ΔEDV>20%                | 24 (21.4%)  | positive                             | OR 1.003, 95%CI [1.001, 1.004] ; p<0.0001                                                                                |                             |  |
|                                                                                                   | 31                                               | day 1, 3, and 7                                          | TTE, 6 mo                                          | ΔEDV or ESV>20%         | 14 (45.2%)  | none, multivariate                   | OR 1.001, 95%CI [0.999, 1.002] ; p=0.2915                                                                                |                             |  |
| <i>linear regression</i>                                                                          |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
| Giallauria et al. (32)                                                                            | 61                                               | baseline                                                 | TTE, 6 mo                                          | changes in EDVI         | NA          | none                                 | OR 1.000, 95%CI [1.000, 1.001] ; p=0.2                                                                                   | pg/mL, enrolment            |  |
| Kercheva et al. (33)                                                                              | 31                                               | day 1, 3, and 7                                          | TTE, 6 mo                                          | ΔEDV or ESV>20%         | 14 (45.2%)  | positive, multivariate               | OR 1.000, 95%CI [1.000, 1.001] ; p=0.008                                                                                 | pg/mL, discharge            |  |
|                                                                                                   |                                                  |                                                          |                                                    |                         |             |                                      | OR 1.000, 95%CI [1.000, 1.001] ; p=0.8                                                                                   |                             |  |
|                                                                                                   |                                                  |                                                          |                                                    |                         |             |                                      | OR 1.001, 95%CI [1.000, 1.001] ; p=0.1 (adjusted)                                                                        |                             |  |
| <i>ROC curve</i>                                                                                  |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
| Reindl et al. (34)                                                                                | 88                                               | unavailable                                              | CMR, 4 mo                                          | ΔEDV≥20 %               | 11 (12.5%)  | positive                             | beta coefficient 0.358 ; t2=0.814 ; p<0.001                                                                              | cut-off value               |  |
|                                                                                                   |                                                  |                                                          |                                                    |                         |             |                                      | beta coefficient 0.005 ; p=0.97                                                                                          | 2155 pg/mL                  |  |
| Devaux et al. (35)                                                                                | 60 (derivation cohort)<br>30 (validation cohort) | day 3-4 (before discharge)                               | TTE, 176 d (derivation)<br>CMR, 121 d (validation) | increase in LVEDV       | 30 (50%)    | none, multivariate                   | AUC 0.74, 95%CI [0.57, 0.90] ; sensitivity 56%, specificity 88%, PPV 41%, NPV 93%<br>OR 9.8, 95%CI [2.4, 39.4] ; p=0.001 |                             |  |
| Lv et al. (36)                                                                                    | 359 (AMI)                                        | at admission                                             | TTE, 6 mo                                          | ΔEDV>10%                | 116 (32.3%) | positive                             | AUC 0.704, 95%CI [0.654, 0.751] ; p<0.001                                                                                | cut-off 1931 ng/L admission |  |
| Reinstadler et al. (37)                                                                           | 123                                              | at admission and daily between day 1 and day 4           | CMR, 4 mo                                          | ΔEDV≥20 %               | 16 (13.0%)  | none                                 | AUC 0.68, 95%CI [0.59, 0.76] sensitivity 50 %, specificity 86 %                                                          |                             |  |
| Xiaozhou et al. (38)                                                                              | 106                                              | unavailable                                              | TTE, 3 mo                                          | ΔEDV>20 %               | 22 (20.8%)  | positive                             | AUC 0.894 ; sensitivity 83.3 %, specificity 81.8 %                                                                       | cut-off 952 pg/mL           |  |
| <i>correlation (Pearson or Spearman)</i>                                                          |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
| Kelly et al. (39)                                                                                 | 404 (81 % STEMI)                                 | pre-discharge                                            | TTE, 10 mo                                         | ΔEDV/ESV, increased EDV | 142 (48.6%) | none                                 | r=0.019 ; p=0.753 (change in EDV)<br>r=0.008 ; p=0.895 (change in ESV)                                                   |                             |  |
| <i>not described</i>                                                                              |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
| Bière et al. (40)                                                                                 | 66                                               | baseline                                                 | CMR, 3 and 12 mo                                   | ΔESV>10%                | 33 (20%)    | none                                 |                                                                                                                          |                             |  |
| Kelly et al. (41)                                                                                 | 91 (85 % STEMI)                                  | 0-12h, 12-24h, 24-48h, and 24h intervals until discharge | TTE, 6 mo                                          | change in LV volumes    | NA          | none                                 |                                                                                                                          |                             |  |
| Manhenke et al. (42)                                                                              | 42                                               | prior to PCI, day 2 and week 1                           | CMR, 2 and 12 mo                                   | none                    | NA          | variable                             |                                                                                                                          |                             |  |
| Mather et al. (43)                                                                                | 48                                               | day 2, day 7                                             | CMR, 1 and 3 mo                                    | none                    | NA          | variable (day 2)<br>positive (day 7) |                                                                                                                          |                             |  |
| <b>Peak NT-proBNP</b>                                                                             |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |
| <i>ROC curve</i>                                                                                  |                                                  |                                                          |                                                    |                         |             |                                      |                                                                                                                          |                             |  |

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|---------------------------------------------------------------------------------------------------|-----|------------------------------------------------------|------------------------|-------------------------------------------|-------------|--------------------------------|------------------------------------------------------------------------------------|-------------------|
| Reinstadler et al. (44)                                                                           | 47  | before PCI, every 6 hours during 24 hours then daily | CMR, 4 mo              | $\Delta$ EDV $\geq$ 20 %                  | 6 (12.8%)   | positive                       | AUC 0.75, 95%CI [0.52, 0.99]<br>sensitivity 66 %, specificity 83 %                 | cut-off 1916 ng/L |
| <i>correlation (Pearson or Spearman)</i>                                                          |     |                                                      |                        |                                           |             |                                |                                                                                    |                   |
| Feistritzer et al. (45)                                                                           | 89  | serially                                             | CMR, 4 mo              | $\Delta$ EDV $\geq$ 20 %                  | 14 (15.7%)  | none<br>none, multivariate     | r=0.204 ; p=0.061<br>r=0.03 ; p=0.787                                              |                   |
| <b>Log NT-proBNP</b>                                                                              |     |                                                      |                        |                                           |             |                                |                                                                                    |                   |
| <i>logistic regression</i>                                                                        |     |                                                      |                        |                                           |             |                                |                                                                                    |                   |
| Kim et al. (46)                                                                                   | 262 | unavailable                                          | TTE, 6 mo              | $\Delta$ EDV $\geq$ 20 %                  | 66 (25.2%)  | positive, multivariate         | OR range : 1.28, 95%CI [1.02, 1.61] ; p=0.03 to 1.34, 95%CI [1.09, 1.64] ; p=0.005 | multiple models   |
| <i>linear regression</i>                                                                          |     |                                                      |                        |                                           |             |                                |                                                                                    |                   |
| Lin et al. (47)                                                                                   | 264 | day 2                                                | TTE, 6 mo              | $\Delta$ EDVI $\geq$ 20 ml/m <sup>2</sup> | unavailable | positive                       | standardized coefficient 2.352 ; p=0.012                                           |                   |
| Liu et al. (48)                                                                                   | 331 | unavailable                                          | TTE, 6 mo              | increase in LVEDVi                        | NA          | positive<br>none, multivariate | coefficient 7.049 ; p=0.006<br>coefficient 2.853 ; p=0.305                         |                   |
| <i>not described</i>                                                                              |     |                                                      |                        |                                           |             |                                |                                                                                    |                   |
| Nilsson et al. (49)                                                                               | 42  | 1 week,                                              | CMR, 1, 3, 6 and 12 mo | none                                      | NA          | positive, multivariate         |                                                                                    |                   |
| <b>proBNP</b>                                                                                     |     |                                                      |                        |                                           |             |                                |                                                                                    |                   |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+</i> |     |                                                      |                        |                                           |             |                                |                                                                                    |                   |
| Khurelsukh et al. (50)                                                                            | 35  | at admission                                         | TTE, 2 and 12 mo       | $\Delta$ EDV $\geq$ 20 %                  | 14 (40%)    | none                           | 587 $\pm$ 1311 vs. 626 $\pm$ 1280 ; p=0.24                                         | pg/mL             |
| Andrejic et al. (51)                                                                              | 57  | during PCI                                           | TTE, 6 mo              | $\Delta$ ESV $\geq$ 20 %                  | 22 (38.6%)  | none                           | 250 [179, 207] vs. 1577 [309.5, 4926] ; p=0.182                                    | pg/mL             |

Table 2

|                                                                                                   | sample size | biomarker assessment                               | follow-up imaging | definition of LVR                                | LVR         | correlation         | relationship                                           | comments                         |
|---------------------------------------------------------------------------------------------------|-------------|----------------------------------------------------|-------------------|--------------------------------------------------|-------------|---------------------|--------------------------------------------------------|----------------------------------|
| <b>Hemoglobin</b>                                                                                 |             |                                                    |                   |                                                  |             |                     |                                                        |                                  |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+</i> |             |                                                    |                   |                                                  |             |                     |                                                        |                                  |
| Barbaro et al. (52)                                                                               | 55          | baseline                                           | TTE, 2 mo         | $\Delta\text{ESV} \geq 15\%$                     | 13 (24%)    | none                | 13.2 vs. 13.2; p=0.80                                  | g/dL                             |
| Na et al. (28)                                                                                    | 208         | unavailable                                        | TTE, 6 mo         | $\Delta\text{EDV} > 20\%$                        | 53 (25.5%)  | none                | 14.8 $\pm$ 1.8 vs. 14.6 $\pm$ 1.8; p=0.515             | g/dL                             |
| Wu et al. (24)                                                                                    | 104         | before and after PCI                               | TTE, 6 mo         | $\geq 15\%$ decrease in ESV (reverse remodeling) | 56 (53.8%)  | reverse             | 13.6 $\pm$ 1.4 vs. 13.7 $\pm$ 1.5; p=0.19              | g/dL                             |
| Andrejic et al. (51)                                                                              | 57          | during PCI                                         | TTE, 6 mo         | $\Delta\text{ESV} \geq 20\%$                     | 22 (38.6%)  | none                | 142 [132, 142] vs. 130.5 [112.5, 154.5]; p=0.397       | g/L                              |
| <i>linear regression</i>                                                                          |             |                                                    |                   |                                                  |             |                     |                                                        |                                  |
| Lin et al. (47)                                                                                   | 264         | day 2                                              | TTE, 6 mo         | $\Delta\text{EDV} > 20 \text{ ml/m}^2$           | unavailable | positive            | standardized coefficient : 1.333; p=0.007              |                                  |
| Liu et al. (48)                                                                                   | 331         | unavailable                                        | TTE, 6 mo         | increase in EDVi                                 | NA          | positive            | coefficient : 1.464; p=0.026                           |                                  |
|                                                                                                   |             |                                                    |                   |                                                  |             | none, multivariate  | coefficient : 0.394; p=0.567                           |                                  |
| <b>White blood cells</b>                                                                          |             |                                                    |                   |                                                  |             |                     |                                                        |                                  |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+</i> |             |                                                    |                   |                                                  |             |                     |                                                        |                                  |
| Abdel Hamid et al. (53)                                                                           | 62          | within 24 hours                                    | TTE, 1 mo         | $\Delta\text{EDV} \geq 20\%$                     | 16 (26%)    | none                | 11.6 $\pm$ 4.4 vs. 14.0 $\pm$ 3.8; p=0.065             | 10 <sup>3</sup> cells/mL         |
| Bonios et al. (54)                                                                                | 42          | baseline                                           | TTE, 3 mo         | $\Delta\text{ESV} > 15\%$                        | 13 (31%)    | positive            | 11.5 $\pm$ 3.0 vs. 16.0 $\pm$ 3.0; p<0.05              | cells/L                          |
| Garcia et al. (27)                                                                                | 64          | 48h [IQR 24:72]                                    | CMR, 3 and 12 mo  | $\Delta\text{ESV} > 10\%$                        | NA          | positive            | 10.346 $\pm$ 3.626 vs. 12.028 $\pm$ 2.593; p=0.028     |                                  |
| Andrejic et al. (51)                                                                              | 57          | during PCI                                         | TTE, 6 mo         | $\Delta\text{ESV} \geq 20\%$                     | 22 (38.6%)  | positive            | 9.0 [8.3, 11.7] vs. 9.5 [9.17, 12.6]; p=0.016; Z=2.404 | 10 <sup>12</sup> /L              |
| Garcia et al. (27)                                                                                | 64          | 48h [IQR 24:72]                                    | CMR, 3 and 12 mo  | $\Delta\text{ESV} > 10\%$                        | NA          | positive            | 7.596 $\pm$ 3.822 vs. 9.035 $\pm$ 3.036; p<0.001       | neutrophils                      |
| Caldeney et al. (55)                                                                              | 227         | day 1, day 7, 6 months                             | CMR, 6 mo         | $\Delta\text{EDV} \geq 20\%$                     | 29 (16%)    | none                | 0.59 $\pm$ 0.55 vs. 0.60 $\pm$ 0.26; p=0.924           | G/L, day 1                       |
|                                                                                                   |             |                                                    |                   |                                                  |             | none                | 0.79 $\pm$ 0.98 vs. 1.19 $\pm$ 2.09; p=0.210           | G/L, day 7                       |
|                                                                                                   |             |                                                    |                   |                                                  |             |                     |                                                        | monocytes                        |
| <i>logistic regression</i>                                                                        |             |                                                    |                   |                                                  |             |                     |                                                        |                                  |
| Bochenek et al. (56)                                                                              | 66          | Upon admission, 6, 12 and 24h                      | TTE, 3 mo         | $\Delta\text{EDV} > 20\%$                        | 22 (33%)    | positive, bivariate | OR 1.31, 95%CI [1.08, 1.58]; p=0.01                    | per 1/L                          |
| Liu et al. (30)                                                                                   | 198         | day 5                                              | TTE, 12 mo        | $\Delta\text{EDV} \geq 20\%$                     | 56 (28.3%)  | positive            | OR 1.065, 95%CI [1.001, 1.133]; p=0.0467               |                                  |
|                                                                                                   |             |                                                    |                   |                                                  |             | none, multivariate  | OR 0.955, 95%CI [0.857, 1.065]; p=0.4101               |                                  |
| Swiatkiewicz et al. (17)                                                                          | 198         | at admission, 24 hours                             | TTE, 6 mo         | $\Delta\text{EDV} > 20\%$                        | 55 (27.8%)  | none                | OR 1.10, 95%CI [0.97, 1.22]; p=0.068                   | admission at 24h                 |
|                                                                                                   |             |                                                    |                   |                                                  |             | none                | OR 1.09, 95%CI [0.97, 1.23]; p=NS                      | per 10 <sup>3</sup> increase     |
| Aoki et al. (57)                                                                                  | 131         | at presentation and every 24 h for at least 5 days | LVG, 6 mo         | $\Delta\text{EDV} \geq 10\%$                     | 48 (37%)    | positive            | p=0.017                                                | cut-off $\geq 12000/\text{mm}^3$ |
|                                                                                                   |             |                                                    |                   |                                                  |             | none, multivariate  | OR 1.198 95%CI [0.196, 7.333]; p=0.845                 | Peak WBC                         |
| Aoki et al. (57)                                                                                  | 131         | at presentation and every 24 h for at least 5 days | LVG, 6 mo         | $\Delta\text{EDV} \geq 10\%$                     | 48 (37%)    | positive            | p=0.082                                                | cut-off $\geq 8900/\text{mm}^3$  |
|                                                                                                   |             |                                                    |                   |                                                  |             | none, multivariate  | OR 0.412, 95%CI [0.07, 2.404]; p=0.324                 | peak neutrophils                 |
| Aoki et al. (57)                                                                                  | 131         | at presentation and every 24 h for at least 5 days | LVG, 6 mo         | $\Delta\text{EDV} \geq 10\%$                     | 48 (37%)    | positive            | p=0.001                                                | cut-off $\geq 830/\text{mm}^3$   |
|                                                                                                   |             |                                                    |                   |                                                  |             | none, multivariate  | OR 2.741, 95%CI [0.995, 7.554]; p=0.051                | peak monocytes                   |
| <i>linear regression</i>                                                                          |             |                                                    |                   |                                                  |             |                     |                                                        |                                  |
| Lin et al. (47)                                                                                   | 264         | day 2                                              | TTE, 6 mo         | $\Delta\text{EDV} > 20 \text{ ml/m}^2$           | unavailable | positive            | standardized coefficient : 1.099; p=0.042              |                                  |

|                                  |                    |                                                |            |                         |            |                                    |                                                                                                    |
|----------------------------------|--------------------|------------------------------------------------|------------|-------------------------|------------|------------------------------------|----------------------------------------------------------------------------------------------------|
| Zaliadunyte-Pekstone et al. (58) | 141                | unavailable                                    | TTE, 4 mo  | $\Delta$ EDV $\geq$ 20% | 49 (34.8%) | positive<br>positive, multivariate | OR 1.16, 95%CI [1.00, 1.35] ; p=0.038<br>OR 1.12, 95CI [1.00, 1.28] ; p=0.04                       |
| Liu et al. (48)                  | 331                | unavailable                                    | TTE, 6 mo  | increase in EDVi        | NA         | none<br>none, multivariate         | coefficient : 0.694 ; p=0.058<br>coefficient : 0.266 ; p=0.447                                     |
| ROC curve                        |                    |                                                |            |                         |            |                                    |                                                                                                    |
| Karuzas et al. (59)              | 75                 | every 6 h after admission until<br>peak values | TTE, 6 mo  | $\Delta$ EDV $\geq$ 15% | 22 (29.3%) | none                               | AUC 0.497 ; p=0.567 ; cut-off value 13.4x10 <sup>9</sup> /L<br>sensitivity 28 % ; specificity 61 % |
| not described                    |                    |                                                |            |                         |            |                                    |                                                                                                    |
| Bauters et al. (23)              | 226<br>(Q-wave MI) | at admission                                   | TTE, 12 mo | change in EDV           | NA         | positive                           |                                                                                                    |

Table 3.

| sample size                                                                                        | biomarker assessment | follow-up imaging                               | definition of LVR                   | LVR                                                      | correlation           | relationship                                     | comments                                                                                                                               |
|----------------------------------------------------------------------------------------------------|----------------------|-------------------------------------------------|-------------------------------------|----------------------------------------------------------|-----------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| <b>Glucose</b>                                                                                     |                      |                                                 |                                     |                                                          |                       |                                                  |                                                                                                                                        |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR +</i> |                      |                                                 |                                     |                                                          |                       |                                                  |                                                                                                                                        |
| Buono et al. (60)                                                                                  | 109                  | once daily during hospitalization               | TTE, 17 mo                          | ΔEDV ≥ 20%<br>≥ 15% decrease in ESV (reverse remodeling) | 30 (28%)              | none                                             | 134 ± 62 vs. 125 ± 46 ; p=0.507<br>mg/dL, fasting                                                                                      |
| Wu et al. (24)                                                                                     | 104                  | in the morning of the first day after admission | TTE, 6 mo                           | ΔEDV ≥ 20%<br>≥ 15% decrease in ESV (reverse remodeling) | 56 (53.8%)<br>reverse | none                                             | 8.44 ± 4.96 vs. 8.42 ± 4.63 ; p=0.50<br>mmol/L, fasting                                                                                |
| Barbato et al. (52)                                                                                | 55                   | baseline                                        | TTE, 2 mo                           | ΔESV ≥ 15 %                                              | 13 (24%)              | none                                             | 126 ± 55 vs. 129 ± 29 ; p=0.9<br>mg/dL                                                                                                 |
| Reindl et al. (61)                                                                                 | 143                  | unavailable                                     | CMR, 4 mo                           | ΔEDV ≥ 15%                                               | 29 (20%)              | none                                             | 134 [114, 153] vs. 136 [118, 165] ; p=0.36<br>mg/dL                                                                                    |
| Swiatkiewicz et al. (17)                                                                           | 198                  | at admission                                    | TTE, 6 mo                           | ΔEDV > 20%                                               | 55 (27.8%)            | none                                             | 7.4 [6.7, 9.2] vs. 7.8 [6.8, 9.6] ; p=NS<br>mmol/L, admission                                                                          |
| Turkoğlu et al. (21)                                                                               | 255                  | at admission, 24 hours                          | TTE, 6 mo                           | ΔEDV ≥ 20%                                               | 60 (23.5%)            | none                                             | 145.9 ± 70.0 vs. 150.0 ± 89.4 ; p=0.722<br>mg/dL                                                                                       |
| Andrejic et al. (51)                                                                               | 57                   | during PCI                                      | TTE, 6 mo                           | ΔESV ≥ 20%                                               | 22 (38.6%)            | none                                             | 6.00 [5.10, 8.10] vs. 5.50 [4.63, 9.60] ; p=0.525 ;<br>Z=0.635                                                                         |
| <i>logistic regression</i>                                                                         |                      |                                                 |                                     |                                                          |                       |                                                  |                                                                                                                                        |
| Aoki et al. (57)                                                                                   | 131                  | at presentation                                 | LVG, 6 mo                           | ΔEDV ≥ 10%                                               | 48 (37%)              | positive<br>positive, multivariate               | p=0.003<br>OR 3.020, 95%CI [1.329, 6.866] ; p=0.008<br>cut-off 130 mg/dL, fasting                                                      |
| Golbbara et al. (16)                                                                               | 69                   | at admission                                    | CMR, 7 mo                           | ΔEDV ≥ 20%                                               | 18 (26.1%)            | none<br>none                                     | OR 1.007, 95%CI [0.596, 1.018] ; p=0.196<br>OR 1.016, 95%CI [0.599, 1.034] ; p=0.065<br>per 1 mg/dL                                    |
| Joyce et al. (62)                                                                                  | 964                  | unavailable                                     | TTE, 6 mo                           | ΔEDV ≥ 20%                                               | 296 (30.7%)           | positive<br>none multivariate                    | OR 1.08, 95%CI [1.03, 1.13] ; p=0.001<br>p=NS<br>mmol/L                                                                                |
| Piestrzeniewicz et al. (63)                                                                        | 75                   | at admission                                    | TTE, 12 mo                          | ΔEDV ≥ 20%                                               | 15 (20%)              | positive                                         | OR 1.0228, 95%CI [1.008, 1.0378] ; p=0.0024                                                                                            |
| Urbano-Moral et al. (31)                                                                           | 112                  | during PCI                                      | TTE, 6 mo                           | ΔEDV ≥ 20%                                               | 24 (21.4%)            | none                                             | OR 0.998, 95%CI [0.990, 1.006] ; p=0.60<br>at enrolment                                                                                |
| <i>linear regression</i>                                                                           |                      |                                                 |                                     |                                                          |                       |                                                  |                                                                                                                                        |
| Bauters et al. (64)                                                                                | 137                  | at admission                                    | TTE, 12 mo                          | ΔEDV > 20%                                               | 44 (32%)              | positive, multivariate<br>positive, multivariate | beta coefficient 0.218 ; p=0.009<br>beta coefficient 0.173 ; p=0.03<br>cut-off glucose admission 7 mM<br>glucose : quantitative values |
| <i>correlation (Pearson or Spearman)</i>                                                           |                      |                                                 |                                     |                                                          |                       |                                                  |                                                                                                                                        |
| Feistritzer et al. (45)                                                                            | 89                   | at admission                                    | CMR, 4 mo                           | ΔEDV ≥ 20%                                               | 14 (15.7%)            | none                                             | r=0.020 ; p=0.852<br>mg/dL, admission                                                                                                  |
| <i>not described</i>                                                                               |                      |                                                 |                                     |                                                          |                       |                                                  |                                                                                                                                        |
| Nicolau et al. (65)                                                                                | 52                   | at admission                                    | Radionuclide ventriculography, 6 mo | none                                                     | NA                    | positive                                         |                                                                                                                                        |

Table 4.

|                                                                                                   | sample size     | biomarker assessment                                                    | follow-up imaging | definition of LYR            | LYR        | correlation            | relationship                                                                           | comments                                         |
|---------------------------------------------------------------------------------------------------|-----------------|-------------------------------------------------------------------------|-------------------|------------------------------|------------|------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------|
| <b>Peak C-reactive protein</b>                                                                    |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| <i>logistic regression</i>                                                                        |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Aoki et al. (57)                                                                                  | 131             | at presentation and every 24 h for at least 5 days                      | LV, 6 mo          | $\Delta\text{EDV} \geq 10\%$ | 48 (37%)   | none                   | $p=0.095$<br>OR 1.417, 95%CI [0.606, 3.316]; $p=0.422$                                 | cut-off 10.2 mg/dL                               |
| Golbana et al. (16)                                                                               | 69              | at admission, every 3h during 24 h, every 6h the next 2 days then daily | CMR, 7 mo         | $\Delta\text{EDV} \geq 20\%$ | 18 (26.1%) | none, multivariate     | OR 1.019, 95%CI [0.887, 1.171]; $p=0.787$<br>OR 1.038, 95%CI [0.835, 1.291]; $p=0.736$ | per 1mg/dL                                       |
| <i>correlation (Pearson or Spearman)</i>                                                          |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Feistritzer et al. (45)                                                                           | 89              | serially                                                                | CMR, 4 mo         | $\Delta\text{EDV} \geq 20\%$ | 14 (15.7%) | none                   | $r=0.042$ ; $p=0.698$                                                                  | mg/dL                                            |
| <b>C-reactive protein</b>                                                                         |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LYR- vs. LYR+</i> |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Caldeney et al. (55)                                                                              | 227             | day 1, day 7                                                            | CMR, 6 mo         | $\Delta\text{EDV} \geq 20\%$ | 29 (16%)   | none                   | 87.8±185.9 vs. 76.8±117.0; $p=0.781$                                                   | ng/mL, day 1                                     |
| Zaladonnyre-Peksiene et al. (58)                                                                  | 141             | unavailable                                                             | TTE, 4 mo         | $\Delta\text{EDV} \geq 20\%$ | 49 (34.8%) | none                   | 75.7±173.6 vs. 52.8±103.7; $p=0.535$                                                   | ng/mL, day 7                                     |
| Garcia et al. (27)                                                                                | 64              | 48h [IQR 24;72]                                                         | CMR, 3 and 12 mo  | $\Delta\text{ESV} > 10\%$    | NA         | positive               | 4.7 [2.85, 16.32] vs. 10.58 [2.2, 24.5]; $p=NS$                                        | mg/L                                             |
| <i>logistic regression</i>                                                                        |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Dominguez-Rodriguez et al. (15)                                                                   | 108             | before primary PCI                                                      | TTE, 12 mo        | $\Delta\text{EDV} > 20\%$    | 21 (19%)   | none                   | OR 1.369, 95%CI [0.638, 2.940]; $p=0.42$                                               | mg/L                                             |
| Liu et al. (30)                                                                                   | 198             | day 5                                                                   | TTE, 12 mo        | $\Delta\text{EDV} \geq 20\%$ | 56 (28.3%) | positive               | OR 1.218, 95%CI [1.077, 1.377]; $p=0.0017$                                             |                                                  |
| Pietrzewicz et al. (63)                                                                           | 75              | unavailable                                                             | TTE, 12 mo        | $\Delta\text{EDV} \geq 20\%$ | 15 (20%)   | positive               | OR 1.012, 95%CI [0.803, 1.275]; $p=0.3222$                                             |                                                  |
| Swiatkiewicz et al. (17)                                                                          | 198             | at admission, 24 hours, discharge                                       | TTE, 6 mo         | $\Delta\text{EDV} > 20\%$    | 55 (27.8%) | positive               | OR 1.145, 95%CI [1.037, 1.264]; $p=0.0072$                                             | admission                                        |
|                                                                                                   |                 |                                                                         |                   |                              |            | positive               | OR 2.09, 95%CI [0.60, 14.92]; $p=NS$                                                   | 24h admission                                    |
|                                                                                                   |                 |                                                                         |                   |                              |            | positive               | OR 1.29, 95%CI [1.08, 1.56]; $p<0.01$                                                  | discharge                                        |
|                                                                                                   |                 |                                                                         |                   |                              |            | positive, multivariate | OR 1.05, 95%CI [0.86, 1.30]; $p=NS$                                                    | discharge                                        |
|                                                                                                   |                 |                                                                         |                   |                              |            |                        | OR 1.29, 95%CI [1.04, 1.60]; $p<0.05$                                                  | for a 10 mg/L increase                           |
| <i>linear regression</i>                                                                          |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Fertin et al. (19)                                                                                | 226 (Q-wave MI) | at discharge (day 3 to day 7)                                           | TTE, 12 mo        | $\Delta\text{EDV} > 20\%$    | 87 (38%)   | positive               | beta coefficient: 0.185; $p=0.006$                                                     | baseline                                         |
| <b>ROC curve</b>                                                                                  |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Kanuzas et al. (59)                                                                               | 75              | every 6 h after admission until peak values                             | TTE, 6 mo         | $\Delta\text{EDV} \geq 15\%$ | 22 (29.3%) | none                   | AUC 0.601; cut-off 13.9 mg/L; $p=0.108$<br>sensitivity 48 %, specificity 78 %          |                                                  |
| <i>correlation (Pearson or Spearman)</i>                                                          |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Schoos et al. (66)                                                                                | 55              | day 1-2, day 4, day 7                                                   | CMR, 6 mo         | change in EDV and/or ESV     | NA         | none                   | $R=0.073$ ; $p=0.61$<br>$R=-0.028$ ; $p=0.92$                                          | for $\Delta\text{ESV}$<br>for $\Delta\text{EDV}$ |
| <b>Peak high-sensitivity C-reactive protein</b>                                                   |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| <i>logistic regression</i>                                                                        |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Reindl et al. (61)                                                                                | 143             | unavailable                                                             | CMR, 4 mo         | $\Delta\text{EDV} \geq 15\%$ | 29 (20%)   | positive               | OR 4.39, 95%CI [1.86, 10.31]; $p=0.001$                                                | cut-off 31 mg/L                                  |
|                                                                                                   |                 |                                                                         |                   |                              |            | positive, multivariate | OR 2.66, 95%CI [1.05, 6.71]; $p=0.04$                                                  |                                                  |
| <i>linear regression</i>                                                                          |                 |                                                                         |                   |                              |            |                        |                                                                                        |                                                  |
| Reindl et al. (67)                                                                                | 102             | unavailable                                                             | CMR, 4 mo         | $\Delta\text{EDV} \geq 20\%$ | 15 (14.7%) | positive               | OR 4.29, 95%CI [1.26, 14.56]; $p=0.02$                                                 | cut-off 23 mg/L                                  |
|                                                                                                   |                 |                                                                         |                   |                              |            | positive, multivariate | $p=NS$                                                                                 |                                                  |

| High-sensitivity C-reactive protein                                                        |                   |                                                |                  |                                           |             |                                |                                                                                                                                                                     |                                                          |  |  |
|--------------------------------------------------------------------------------------------|-------------------|------------------------------------------------|------------------|-------------------------------------------|-------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|--|--|
| between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+ |                   |                                                |                  |                                           |             |                                |                                                                                                                                                                     |                                                          |  |  |
| Buono et al. (60)                                                                          | 109               | day 2, after a 12-hour overnight fast          | TTE, 17 mo       | ΔEDV≥20%                                  | 30 (28%)    | none                           | 11±18 vs. 17±25 ; p=0.281                                                                                                                                           | mg/L                                                     |  |  |
| Hsu et al. (10)                                                                            | 97<br>(61% STEMI) | at first 3 days                                | TTE, 6 mo        | ΔEDV>20%                                  | 24 (32.9%)  | none                           | 33.3±36.2 vs. 37.5±44.2 ; p=0.662                                                                                                                                   | mg/L                                                     |  |  |
| Khurelsukh et al. (50)                                                                     | 35                | at admission                                   | TTE, 2 and 12 mo | ΔEDV≥20% (2 mo)                           | 14 (40%)    | positive                       | 0.18±0.20 vs. 0.38±0.38 ; p=0.046                                                                                                                                   | ng/dL                                                    |  |  |
| Na et al. (28)                                                                             | 208               | unavailable                                    | TTE, 6 mo        | ΔEDV>20%                                  | 53 (25.5%)  | none                           | 0.94±2.40 vs. 0.67±1.14 ; p=0.276                                                                                                                                   | mg/L                                                     |  |  |
| Choe et al. (68)                                                                           | 1237              | unavailable                                    | TTE, 6 mo        | >10% decrease in ESV (reverse remodeling) | 466 (37.7%) | positive                       | 0.6 [0.2, 0.8] vs. 0.7 [0.3, 0.6] ; p=0.046                                                                                                                         | mg/L                                                     |  |  |
| Wu et al. (24)                                                                             | 104               | before and after PCI                           | TTE, 6 mo        | ≥15% decrease in ESV (reverse remodeling) | 56 (53.8%)  | none (propensity-matched)      | 0.6 [0.1, 2.9] vs. 0.8 [0.3, 4.6] ; p=0.111                                                                                                                         | mg/L                                                     |  |  |
| Andrejic et al. (51)                                                                       | 57                | during PCI                                     | TTE, 6 mo        | ΔEDV≥20%                                  | 22 (38.6%)  | positive                       | 0.57±0.34 vs. 0.56±0.39 ; p=0.87                                                                                                                                    | mg/L                                                     |  |  |
| logistic regression                                                                        |                   |                                                |                  |                                           |             |                                |                                                                                                                                                                     |                                                          |  |  |
| Urbano-Moral et al. (31)                                                                   | 112               | at discharge                                   | TTE, 6 mo        | ΔEDV≥20%                                  | 24 (21.4%)  | positive                       | 3.4 [1.35, 7.3] vs. 13.50 [4.70, 87.20] ; p=0.035 ; Z=2.112                                                                                                         | mg/L                                                     |  |  |
| ROC curve                                                                                  |                   |                                                |                  |                                           |             |                                |                                                                                                                                                                     |                                                          |  |  |
| Reindl et al. (34)                                                                         | 88                | unavailable                                    | CMR, 4 mo        | ΔEDV≥20%                                  | 11 (12.5%)  | positive                       | OR 1.022, 95%CI [1.006, 1.038] ; p=0.006<br>OR 1.016, 95%CI [1.000, 1.032] ; p=0.04<br>OR 1.040, 95%CI [1.000, 10.081] ; p=0.04                                     | mg/L, discharge, unadjusted<br>mg/L, discharge, adjusted |  |  |
| Reinstadler et al. (37)                                                                    | 123               | at admission and daily between day 1 and day 4 | CMR, 4 mo        | ΔEDV≥20%                                  | 16 (13.0%)  | none                           | AUC 0.68, 95%CI [0.52, 0.84] ; cut-off 23mg/L<br>Se 73 % ; Sp 63 % ; PPV 23 % ; NPV 94 %<br>p=NS                                                                    | admission                                                |  |  |
| Xiaozhou et al. (38)                                                                       | 106               | unavailable                                    | TTE, 3 mo        | ΔEDV≥20%                                  | 22 (20.8%)  | positive                       | AUC 0.63, 95%CI [0.54, 0.72] ; cut-off 22.5 mg/L<br>sensitivity 88 % , specificity 48 %<br>AUC 0.825, cut-off 12.4 pg/mL<br>sensitivity 76.2 % , specificity 81.8 % |                                                          |  |  |
| not described                                                                              |                   |                                                |                  |                                           |             |                                |                                                                                                                                                                     |                                                          |  |  |
| Manhenke et al. (42)                                                                       | 42                | prior to PCI, day 2, week 1                    | CMR, 2 and 12 mo | none                                      | NA          | variable                       |                                                                                                                                                                     |                                                          |  |  |
| Mather et al. (43)                                                                         | 48                | day 2, day 7                                   | CMR, 1 and 3 mo  | none                                      | NA          | positive (day 2), multivariate |                                                                                                                                                                     |                                                          |  |  |
| log high-sensitivity C-reactive protein                                                    |                   |                                                |                  |                                           |             |                                |                                                                                                                                                                     |                                                          |  |  |
| logistic regression                                                                        |                   |                                                |                  |                                           |             |                                |                                                                                                                                                                     |                                                          |  |  |
| Hsiao et al. (25)                                                                          | 54                | immediately, 8 hours, 16 hours                 | TTE, 3 and 6 mo  | ΔESV>15% (6 mo)                           | 19 (35.2%)  | none                           |                                                                                                                                                                     |                                                          |  |  |

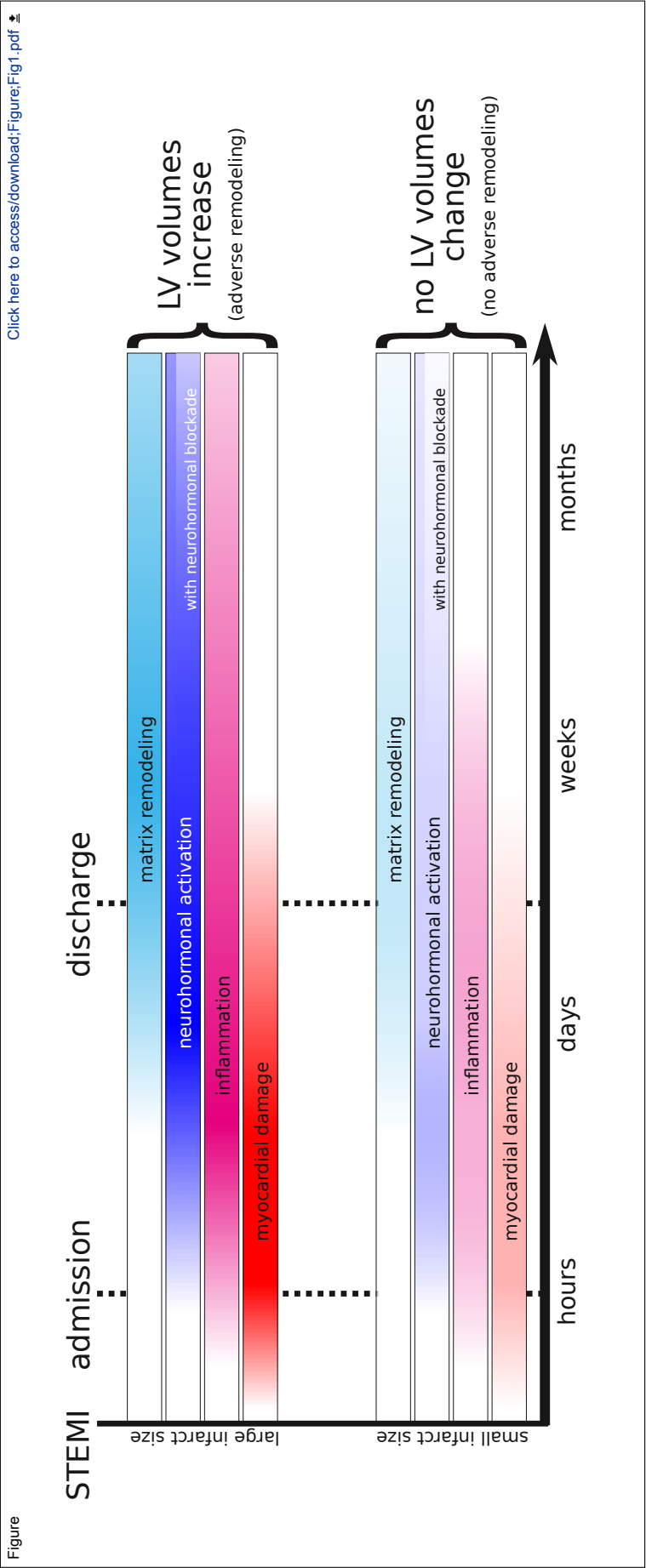


|                                          |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
|------------------------------------------|--------------------|--------------------------------------------------------------------------|------------------|--------------------------------------|----------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Urbano-Moral et al. (31)                 | 112                | at discharge                                                             | TTE, 6 mo        | $\Delta\text{EDV} \geq 20\%$         | 24 (21.4%)     | positive<br>positive, multivariate | OR 1.001, 95%CI [1.000, 1.001]; $p=0.004$<br>OR 1.000, 95%CI [1.000, 1.001]; $p=0.03$<br>OR 1.001, 95%CI [1.000, 1.001]; $p=0.04$ | ng/mL<br>ng/mL, unadjusted<br>ng/mL, adjusted           |
| <i>linear regression</i>                 |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Fertin et al. (69)                       | 226<br>(Q-wave MI) | at discharge (day 3 to day 7)                                            | TTE, 12 mo       | $\Delta\text{EDV} > 20\%$            | 87 (38%)       | positive (baseline)                | regression coefficient: 0.153; $p=0.02$<br>standardized beta coefficient: 0.131; $p=0.07$                                         |                                                         |
| <i>correlation (Pearson or Spearman)</i> |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Cerisano et al. (70)                     | 106                | early after PCI and at days 1, 7                                         | TTE, 6 mo        | change in EDVi                       | NA             | none                               |                                                                                                                                   |                                                         |
| Kelly et al. (41)                        | 91<br>(85 % STEM)  | 0-12 h, 12-24 h, 24-48 h, and 24 h intervals thereafter, until discharge | TTE, 6 mo        | change in LV volumes                 | NA             | positive<br>positive, multivariate | $r=0.3$ ; $p=0.016$<br>$p=0.007$<br>$p=0.005$                                                                                     | change in EDV<br>change in EDV<br>change in EDV         |
| Kelly et al. (39)                        | 404<br>(81 % STEM) | within 24 h of admission                                                 | TTE, 10 mo       | change in EDV and ESV, increased EDV | 142<br>(48.6%) | positive                           | $r=0.174$ ; $p=0.005$<br>$r=0.04$ ; $p=0.520$                                                                                     | change in EDV<br>change in EDV                          |
| Nilsson et al. (71)                      | 46                 | before PCI, 12 hours, 24 hours and 48 hours                              | CMR, 4 mo        | change in EDVi and ESVi              | NA             | positive<br>none                   | $r$ range from -0.288 to 0.033; $p=NS$<br>$r$ range from -0.228 to -0.027; $p=NS$                                                 | change in EDV<br>change in EDV                          |
| Webb et al. (72)                         | 32<br>(84 % STEM)  | at enrollment, , days 2 to 5                                             | TTE, 3 and 6 mo  | change in EDV                        | NA             | positive                           | $r=0.63$ ; $p=0.03$                                                                                                               | change in EDV                                           |
| <i>not described</i>                     |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Manhenke et al. (42)                     | 42                 | prior to PCI, day 2, week 1                                              | CMR, 2 and 12 mo | none                                 | NA             | none                               |                                                                                                                                   |                                                         |
| <b>TIMP-1</b>                            |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| <i>linear regression</i>                 |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Fertin et al. (69)                       | 226 (Q-wave MI)    | at discharge (day 3 to day 7)                                            | TTE, 12 mo       | $\Delta\text{EDV} > 20\%$            | 87 (38%)       | none                               | regression coefficient: 0.116; $p=NS$                                                                                             |                                                         |
| <i>correlation (Pearson or Spearman)</i> |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Cerisano et al. (70)                     | 106                | early after PCI and at days 1, 7                                         | TTE, 6 mo        | unavailable                          | NA             | none<br>none<br>none               | $r=-0.06$ ; $p=0.60$<br>$r=-0.03$ ; $p=0.81$<br>$r=-0.12$ ; $p=0.28$                                                              | baseline<br>day 1<br>day 7                              |
| Kelly et al. (39)                        | 404 (81 % STEM)    | pre-discharge                                                            | TTE, 10 mo       | change in EDV and ESV, increased EDV | 142<br>(48.6%) | variable                           | $r=0.124$ ; $p=0.036$                                                                                                             | change in EDV<br>change in EDV                          |
| Nilsson et al. (71)                      | 46                 | before PCI, 12 hours, 24 hours and 48 hours                              | CMR, 4 mo        | change in EDVi and ESVi              | NA             | variable<br>none                   | $r=-0.305$ ; $p<0.05$ ; $p=NS$ otherwise<br>$r$ range from -0.261 to -0.076; $p=NS$                                               | change in EDV<br>at 48h, change in EDV<br>change in EDV |
| Webb et al. (72)                         | 32<br>(84 % STEM)  | at enrollment, , days 2 to 5                                             | TTE, 3 and 6 mo  | change in EDV                        | NA             | none                               | $r=-0.20$ ; $p>0.20$                                                                                                              |                                                         |
| <i>not described</i>                     |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Manhenke et al. (42)                     | 42                 | prior to PCI, day 2, week 1                                              | CMR, 2 and 12 mo | none                                 | NA             | none                               |                                                                                                                                   |                                                         |
| <b>TIMP-2</b>                            |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| <i>linear regression</i>                 |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Fertin et al. (69)                       | 226<br>(Q-wave MI) | at discharge (day 3 to day 7)                                            | TTE, 12 mo       | $\Delta\text{EDV} > 20\%$            | 87 (38%)       | none                               | regression coefficient: 0.066; $p=NS$                                                                                             |                                                         |
| <i>correlation (Pearson or Spearman)</i> |                    |                                                                          |                  |                                      |                |                                    |                                                                                                                                   |                                                         |
| Cerisano et al. (70)                     | 106                | early after PCI and at days 1, 7                                         | TTE, 6 mo        | change in EDVi                       | NA             | none<br>none<br>negative           | $r=0.09$ ; $p=0.42$<br>$r=0.05$ ; $p=0.63$<br>$r=-0.24$ ; $p=0.03$                                                                | baseline<br>day 1<br>day 7                              |
| Nilsson et al. (71)                      | 46                 | before PCI, 12 hours, 24 hours and 48 hours                              | CMR, 4 mo        | change in EDVi and ESVi              | NA             | none<br>none                       | $r$ range from -0.043 to 0.044; $p=NS$<br>$r$ range from 0.015 to 0.092; $p=NS$                                                   | change in EDV<br>change in EDV                          |

|                                                                                                   |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
|---------------------------------------------------------------------------------------------------|-------------------|------------------------------------------------------|---------------------|-----------------------------------------------------------|------------|----------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Webb et al. (72)                                                                                  | 32<br>(84 % STEM) | at enrollment, days 2 to 5                           | TTE, 3 and<br>6 mo  | change in EDV                                             | NA         | none     | r=-0.24 ; p>0.20                                                                                                                        |
| <i>not described</i>                                                                              |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Manhenke et al. (42)                                                                              | 42                | prior to PCI, day 2, week 1                          | CMR, 2 and<br>12 mo | none                                                      | NA         | none     |                                                                                                                                         |
| <b>N-terminal type I procollagen (PINP)</b>                                                       |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| <i>logistic regression</i>                                                                        |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Urbano-Moral et al. (31)                                                                          | 112               | at discharge                                         | TTE, 6 mo           | $\Delta\text{EDV} \geq 20\%$                              | 24 (21.4%) | none     | OR 1.003, 95%CI [0.969, 1.038] ; p=0.90                                                                                                 |
| <i>not described</i>                                                                              |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Manhenke et al. (42)                                                                              | 42                | prior to PCI, day 2, week 1                          | CMR, 2 and<br>12 mo | none                                                      | NA         | variable | $\mu\text{g/l}$                                                                                                                         |
| <b>N-terminal type III procollagen (PIIINP)</b>                                                   |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+</i> |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Radovan et al. (74)                                                                               | 30                | at admission, day 2, day 4, day 7                    | TTE, 1 and<br>6 mo  | none                                                      | NA         | positive | $\Delta\text{EDV1} = 4.67 \pm 0.95 \text{ mL/m}^2$ (PIINP4 $\leq 4.0 \mu\text{g/L}$ ) vs.<br>$12.84 \pm 1.23 \text{ mL/m}^2$ ; p<0.0001 |
| <i>correlation (Pearson or Spearman)</i>                                                          |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Poulsen et al. (75)                                                                               | 47                | at admission, once a day during the following 3 days | TTE, 3 and<br>12 mo | none                                                      | NA         | positive | r=-0.50 ; p<0.001                                                                                                                       |
| <i>not described</i>                                                                              |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Manhenke et al. (42)                                                                              | 42                | prior to PCI, day 2, week 1                          | CMR, 2 and<br>12 mo | none                                                      | NA         | none     | day 4                                                                                                                                   |
| <b>carboxy-terminal telopeptide of procollagen type I (ICTP)</b>                                  |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| <i>linear regression</i>                                                                          |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Cerisano et al. (18)                                                                              | 56                | day 1, day 3                                         | TTE, 6 mo           | $\Delta\text{LVEDV1} > 2$ times the SD of baseline values | 17 (30%)   | positive | beta coefficient : 1.388 [1.082, 1.781] ; p=0.01                                                                                        |
| <i>not described</i>                                                                              |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Manhenke et al. (42)                                                                              | 42                | prior to PCI, day 2, week 1                          | CMR, 2 and<br>12 mo | none                                                      | NA         | none     | beta coefficient : 2.140 [1.120, 3.550] ; p=0.01                                                                                        |
| <b>carboxy-terminal propeptide of procollagen type (PICP)</b>                                     |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| <i>between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+</i> |                   |                                                      |                     |                                                           |            |          |                                                                                                                                         |
| Cerisano et al. (18)                                                                              | 56                | day 1, day 3                                         | TTE, 6 mo           | $\Delta\text{LVEDV1} > 2$ times the SD of baseline values | 17 (30%)   | none     | 99±31 vs. 86±34 ; p=0.197                                                                                                               |
| Radovan et al. (74)                                                                               | 30                | at admission, day 2, day 4, day 7                    | TTE, 1 and<br>6 mo  | none                                                      | NA         | positive | $\Delta\text{EDV1} = 3.96 \pm 1.01 \text{ mL/m}^2$ (PICP4 $\leq 110.0 \mu\text{g/L}$ ) vs.<br>$8.93 \pm 1.68 \text{ mL/m}^2$ ; p=0.02   |

Table 6.

|                                              | sample size         | biomarker assessment                        | follow-up imaging | definition of LVR                        | LVR        | correlation                                | relationship                                                                                                                                                       | comments                       |
|----------------------------------------------|---------------------|---------------------------------------------|-------------------|------------------------------------------|------------|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>Copeptin</b>                              |                     |                                             |                   |                                          |            |                                            |                                                                                                                                                                    |                                |
| Kelly et al. (91)                            | 274<br>(84 % STEM1) | day 3 to 5                                  | TTE, 5 mo         | change in EDV and ESV                    | 88 (32.1%) | positive                                   | $\Delta$ EDV: $r=0.171$ , $p=0.015$ ; AESV: $r=0.186$ , $p=0.008$ .                                                                                                |                                |
| Reinstadler et al. (44)                      | 47                  | day 2                                       | CMR, 4 mo         | $\Delta$ EDV $\geq 20\%$                 | 6 (12.8%)  | positive                                   | AUC 0.79, 95%CI [0.59, 0.98], cut-off value 16.7 pmol/L sensitivity: 67%; specificity: 88 %                                                                        | pmol/L                         |
| <b>Galectin-3</b>                            |                     |                                             |                   |                                          |            |                                            |                                                                                                                                                                    |                                |
| Di Tano et al. (29)                          | 92                  | Baseline                                    | TTE, 6 mo         | $\Delta$ ESV $\geq 15\%$                 | 26 (28.2%) | positive                                   | OR 1.22, 95%CI [1.09, 1.38]; $p=0.0001$                                                                                                                            | per lng/mL change              |
| Andrejic et al. (51)                         | 57                  | day 1                                       | TTE, 6 mo         | $\Delta$ ESV $\geq 20\%$                 | 22 (38.6%) | positive, multivariate                     | OR 1.22, 95%CI [1.06, 1.39]; $p=0.005$                                                                                                                             |                                |
| <b>Hepatocyte Growth Factor</b>              |                     |                                             |                   |                                          |            |                                            |                                                                                                                                                                    |                                |
| Lambin et al. (76)                           | 226<br>(Q-wave MI)  | at discharge (day 3 to day 7)               | TTE, 12 mo        | increase in EDV and ESV                  | NA         | none                                       | 8.22 $\pm$ 2.34 vs. 10.34 $\pm$ 3.81; $t=2.589$ , $p=0.012$                                                                                                        | ng/mL                          |
| Soeki et al. (77)                            | 40 (AMI)            | at admission, day 7                         | LVG, 3 mo         | $\Delta$ EDVi $\geq 5$ ml/m <sup>2</sup> | 15 (37.5%) | variable                                   | 0.33 $\pm$ 0.08 vs. 0.34 $\pm$ 0.12; $p=0.640$<br>0.47 $\pm$ 0.13 vs. 0.36 $\pm$ 0.09; $p=0.003$                                                                   | ng/mL, day 1<br>ng/mL, day 7   |
| <b>Myeloperoxidase</b>                       |                     |                                             |                   |                                          |            |                                            |                                                                                                                                                                    |                                |
| Nilsson et al. (71)                          | 46                  | before PCI, 12 hours, 24 hours and 48 hours | CMR, 4 mo         | change in EDVi and ESVi                  | NA         | none<br>variable                           | correlation : $r$ range from -0.199 to -0.109; $p=NS$<br>correlation : range from -0.347 to -0.033; $p<0.05$ at 48 hours ( $r=-0.347$ ); $p=NS$ otherwise          | change in EDV<br>change in ESV |
| Stamboul et al. (78)                         | 40                  | before and during PCI                       | CMR, 6 mo         | $\Delta$ ESV $>10\%$                     | 19 (47.5%) | none                                       | MPO $<640$ ng/mL : LVR 6/20 patients vs.<br>MPO $>640$ ng/mL : LVR 13/20 patients; $p=0.066$                                                                       |                                |
| Yunoki et al. (79)                           | 160                 | at admission                                | LVG, 6 mo         | none                                     | NA         | positive                                   | correlation : $r=0.250$ ; $p<0.05$                                                                                                                                 | myeloperoxidase DNA            |
| Helseh et al. (92)                           | 272                 | before and immediately after PCI and day 1  | CMR, 4 mo         | change in EDVi or ESVi                   | NA         | none                                       |                                                                                                                                                                    |                                |
| <b>Osteoprotegerin</b>                       |                     |                                             |                   |                                          |            |                                            |                                                                                                                                                                    |                                |
| Erkol et al. (80)                            | 80                  | at admission                                | TTE, 6 mo         | $\Delta$ EDV $\geq 20\%$                 | 29 (36.3%) | positive                                   | OR 4.07, 95%CI [1.51, 10.94]; $p=0.005$                                                                                                                            | cut-off $>132$ pg/mL           |
| Shetelig et al. (81)                         | 272                 | before and immediately after PCI, day 1     | CMR, 4 mo         | change in EDV                            | NA         | positive, multivariate<br>none             | OR 4.05, 95%CI [1.06, 15.38]; $p=0.04$<br>$\Delta$ EDV : 9.0 (-8.3, 24.8) mL (OPG<median) vs. 9.0 (-7.0, 27.0) mL (OPG $>$ median); $p=0.61$                       |                                |
| <b>ST2 (suppression of tumorigenicity-2)</b> |                     |                                             |                   |                                          |            |                                            |                                                                                                                                                                    |                                |
| Bière et al. (40)                            | 66                  | baseline                                    | CMR, 3 and 12 mo  | $\Delta$ ESV $>10\%$                     | 33 (20%)   | none                                       |                                                                                                                                                                    |                                |
| Kercheva et al. (33)                         | 31                  | day 1, day 3, day 7                         | TTE, 6 mo         | $\Delta$ EDV and/or $\Delta$ ESV $>20\%$ | 14 (45.2%) | positive (day 1 and day 3, none otherwise) | 42 (28, 262) ng/mL vs. 162 (36, 279) ng/mL; $p=0.015$<br>33 (17, 61) ng/mL vs. 81 (29, 191) ng/mL; $p=0.021$<br>25 (14, 44) ng/mL vs. 39 (24, 113) ng/mL; $p>0.05$ | day 1<br>day 3<br>day 7        |



## **Relation entre taux de néprilysine et remodelage ventriculaire gauche**

Les systèmes neuro-hormonaux jouent un rôle fondamental dans la survenue du RVG après SCA. La relation entre certains biomarqueurs en lien avec l'activation neuro-hormonale et le RVG ont déjà été décrits. La néprilysine est une endopeptidase capable de dégrader de nombreux substrats tels que la bradykinine, les peptides natriurétiques ou encore l'adrénomédulline [105, 106]. Son inhibition par le sacubitril, associée à un traitement par valsartan forme ce qu'on appelle un inhibiteur de la néprilysine (angiotensin receptor-neprilysin inhibitor) (ARNI) et a permis de diminuer la mortalité et les réhospitalisations pour IC par rapport à l'enalapril, dans une population de patients ayant une IC à FEVG altérée [107]. L'inhibition du SRAA permet de limiter le RVG [108] et de diminuer la mortalité après un STEMI [109]. Dans ce contexte, l'objectif de ce travail est donc d'étudier la relation entre les niveaux plasmatiques de néprilysine et le RVG au décours d'un STEMI.

Le dosage de néprilysine a été réalisé chez 68 patients de la cohorte RESIST pour lesquels nous disposions de prélèvements sanguins sur tubes EDTA et d'échocardiographies permettant d'évaluer les volumes VG en 3D, à la phase initiale et durant le suivi (7 mois, minimum: 6 mois, maximum: 10 mois). Les taux de néprilysine étaient faibles,  $\leq 125$  pg/mL (point d'entrée de la gamme de dosage) pour 38 patients. Nous avons donc formé un premier groupe de patients ayant un taux plasmatique de néprilysine  $\leq 125$  pg/mL et les trente autres patients ont été répartis dans deux autres groupes en fonction de la médiane des valeurs de néprilysine chez ces patients (valeur médiane: 450 pg/mL).

Les patients ayant les taux les plus élevés de néprilysine avaient aussi la FEVG la plus basse à la phase aiguë ( $39,1\% \pm 6,9\%$  vs.  $46,4\% \pm 8,3\%$  dans le groupe  $\leq 125$  pg/mL et vs  $47,1\% \pm 8,1\%$  dans le groupe intermédiaire [126 – 450 pg/mL],  $p < 0,01$ ). Au cours du suivi, la récupération de la FEVG était meilleure dans le groupe néprilysine  $> 450$  pg/mL, conduisant à l'absence de différence significative sur la FEVG par rapport aux autres groupes au terme du suivi ( $50,4\% \pm 9,9\%$  vs  $53,0\% \pm 8,9\%$  et  $50,6\% \pm 9,7\%$  ;  $p = 0,55$ ). Le taux de néprilysine initial est ainsi positivement associé à un stunning en analyse univariée et multivariée. En revanche, nous n'avons pas mis en évidence de corrélation significative avec le volume télédiastolique ventriculaire gauche ou son évolution au cours du suivi.

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RESEARCH ARTICLE

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# Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction



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## Abstract

**Background:** Left ventricular remodeling following ST-elevation myocardial infarction (STEMI) is associated with poor outcome, including heart failure (HF). Neprilysin inhibition leads to improved outcome in patients with altered left ventricular ejection fraction (LVEF).

**Methods:** We aimed to assess the association between serum levels of neprilysin and left ventricular (LV) volumes, function and remodeling in STEMI patients with successful myocardial reperfusion and no clinical sign of HF. Sixty-eight patients were admitted for STEMI and had both plasma neprilysin measurement at baseline and 3D transthoracic echocardiogram at baseline and after a median follow-up of 7 months. We compared 3 groups: a group with a low-level of plasma neprilysin (< 125 pg/mL, i.e. the lower limit of detection of the assay) and the two other groups were defined as being below or above the median value of the remaining samples.

**Results:** Median age was  $58.5 \pm 12.8$  years and 56 (82.4%) were men. Median LVEF was  $45.0 \pm 8.5\%$ . Baseline characteristics were comparable between groups (low-level of neprilysin group [ $\leq 125$  pg/mL,  $n = 38$ ], medium-level of neprilysin group [ $126-450$  pg/mL,  $n = 15$ ] and a high-level group [ $> 450$  pg/mL,  $n = 15$ ]). At baseline there was a non-significant trend towards lower end-diastolic volume ( $p = 0.07$ ) but significantly lower LVEF in the high neprilysin group ( $46.4 \pm 8.3\%$ ,  $47.1 \pm 8.1\%$  and  $39.1 \pm 6.9\%$ ,  $p < 0.01$ ). At follow-up, the magnitude of LVEF increase was significantly more important in the high neprilysin group compared to the other groups ( $p = 0.022$  for relative change in LVEF and  $6.6 \pm 7.3\%$ ,  $3.6 \pm 9.0\%$  and  $11.3 \pm 8.4\%$ ,  $p = 0.031$  for absolute change in LVEF) resulting in similar LVEF levels at follow-up between all groups ( $53.0 \pm 8.9\%$ ,  $50.6 \pm 9.7\%$  and  $50.4 \pm 9.9\%$ ,  $p = 0.55$ ).

**Conclusions:** Initial high neprilysin levels may identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up. Future studies will have to assess the role of neprilysin in the setting of STEMI and the potential benefit of its blockade.

**Keywords:** Neprilysin, ST-elevation myocardial infarction, Left ventricular remodeling

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## Background

Despite widespread urgent coronary revascularization in the setting of ST-elevation myocardial infarction (STEMI), subsequent left ventricular remodeling (LVR) remains common [1, 2] and associated with mortality, heart failure (HF) and ventricular arrhythmia [3]. LVR is the consequence of cellular and histological modifications, such as myocyte hypertrophy, apoptosis and extracellular matrix remodeling [4]. These phenomena are induced by deleterious adaptive mechanical and neurohormonal responses, including the renin-angiotensin-aldosterone system (RAAS) [5]. Early angiotensin-converting enzyme (ACE) inhibition following STEMI associated with a significant reduction in mortality [6] and decreased LVR through suppression of the activity of the RAAS [7] is to be considered in all STEMI patients [8]. Neprilysin is a neutral endopeptidase that degrades several endogenous vasoactive peptides, such as bradykinin, natriuretic peptides and adrenomedullin [9, 10]. Its inhibition interacts with the RAAS, increasing angiotensin-II blood concentrations as compared with placebo, indicative of blockade of the angiotensin-II receptor type 1 (AT1) receptor [11]. In the PARADIGM-HF trial [12], neprilysin inhibition combined with inhibition of AT1 receptors was superior to ACE inhibition by enalapril in reducing both the risks of death and hospitalization for HF in patients with HF and reduced LVEF. In a recent study, the use of an angiotensin receptor-neprilysin inhibitor yielded a significant decrease in left ventricular (LV) volumes at 4 months in the same HF population [13]. There is no data available about the relationship between baseline neprilysin levels and LVR after STEMI. The aim of the present study was to assess the association between serum levels of neprilysin and LV volumes, function and remodeling in STEMI patients at baseline and 6 ± 1 month follow-up.

## Methods

This study was a prospective, observational multicenter study that included consecutive patients admitted for STEMI and treated with either primary percutaneous coronary intervention (pPCI) or rescue PCI after unsuccessful fibrinolysis therapy, from January 2017 to October 2018. Inclusion criteria were as follows: age ≥ 18 years, chest pain associated with an ECG with ST-segment elevation (either > 1 mm in ≥ 2 contiguous limb leads or > 2 mm in ≥ 2 contiguous precordial leads or new left bundle branch block or new significant Q wave). Criteria for exclusion were unsuccessful revascularization (residual stenosis > 30% in the culprit lesion and/or thrombolysis in myocardial infarction flow < 3), clinical signs of HF as defined by Killip Kimball class ≥ II, non-related heart conditions with estimated life expectancy < 12 months and follow-up planned in another center. Informed consent was obtained from the patients.

The study complied with the Declaration of Helsinki and was approved by the local ethics committee (protocol number A14-D17-VOL.20).

On admission, routine blood samples were drawn and collected in tubes containing lithium heparin, ethylenediaminetetraacetic acid or spray-coated silica, centrifuged for 12 min at 2000 g at room temperature then assayed for routine biological measurement. The remaining plasma and serum were stored at - 80 °C until use. Neprilysin was measured on remaining plasma samples in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (Human Neprilysin DuoSet ELISA, RD systems, Minneapolis, USA) according to the manufacturer's instructions. Data were linearized by plotting the log of neprilysin concentrations versus the log of the optical density and the best fit line was determined by regression analysis. Other measurements specific to the present study included high-sensitivity cardiac troponin I (hs-cTnI) (Dxi Beckman Coulter) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Cobas e-411, Roche). Minimum sensitivity and upper limit of detection were 2.3–27027 pg/mL for hs-cTnI, 5–35000 pg/mL for NT-proBNP, and 125–8000 pg/mL for neprilysin; values higher than the upper limit of detection were manually diluted for neprilysin. The highest intra- and inter-assay coefficients of variation were 3.9 and 5.1% for hs-cTnI and 2.7% and 4.6% for NT-proBNP. The recommended diagnostic threshold for the diagnosis of acute myocardial infarction was hs-cTnI > 17.5 pg/mL.

A total of 94 patients with STEMI underwent successful revascularization during the inclusion period. All included subjects had a complete 3D-transthoracic echocardiogram within 48 h. Transthoracic echocardiograms was planned at 6 months after STEMI, as a part of routine follow-up. All echocardiograms were performed using an ultrasonic device system (EPIQ 7G, Phillips Healthcare, Best, Netherlands) and were obtained by experienced ultrasonographers who were unaware of neprilysin measurement results. A standard imaging protocol was used with 4-chamber, 2-chamber apical, and long and short axis parasternal views. Left ventricle end-diastolic volume (EDV), left ventricle end-systolic volume (ESV) and LVEF were measured with 3D method, using Intellispace Cardiovascular software (Philips Healthcare, Best, Netherlands) and TomTec software (TomTec Imaging Systems GmbH, Unterschleißheim, Germany).

The sample size was estimated based on the assumption of a normal distribution for most variables, either as such or after log-transformation by the inclusion of ≥ 60 patients. The study was designed to compare 3 groups based on the tertiles of neprilysin concentration in our population. However, because of the skewed distribution of neprilysin values, we decided to define the lowest

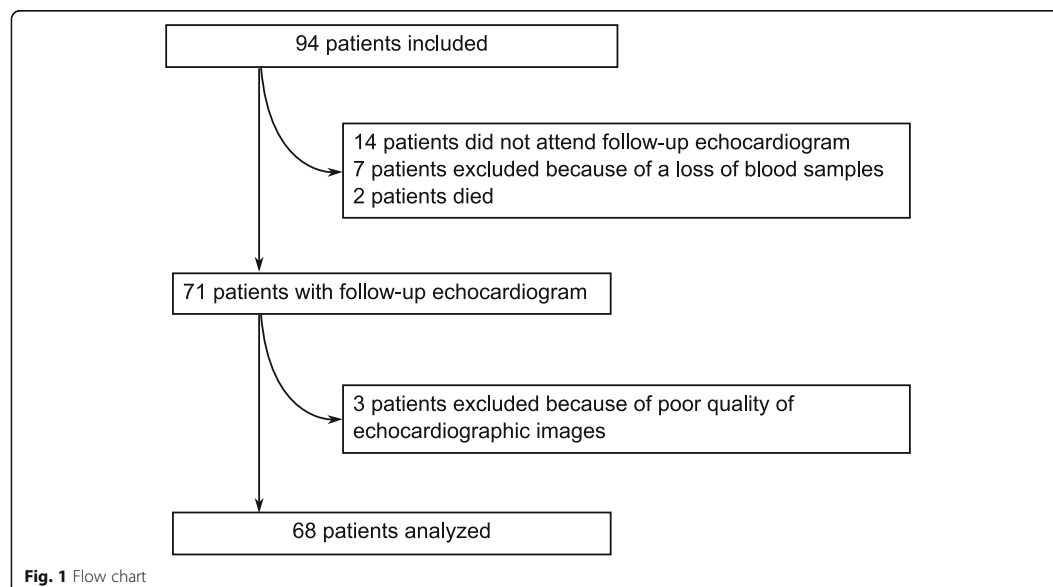
group by those with levels  $< 125$  pg/mL (i.e. the lower limit of detection of the assay) and to divide the remaining patients into two other groups according to median neprilysin concentration value (450 pg/mL) when quantifiable. Qualitative variables are shown as count and frequency (%). Quantitative variables are presented as mean  $\pm$  SD or median and interquartile ranges when they had a skewed distribution. Continuous variables were compared using either ANOVA or Kruskal-Wallis test and categorical variables were compared by the  $\chi^2$  test or Fisher's exact test, where adapted. Biomarkers levels with skewed distribution were log-transformed before being used as continuous variables in statistical analyses. Spearman correlation coefficient was used to assess the correlation between non-normally distributed quantitative parameters. Statistical tests were 2-sided and used a significance threshold of  $p < 0.05$ . All statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

Among the 94 patients with complete 3D-transthoracic echocardiogram at baseline, two patients died during follow-up. Out of the remaining 92 patients, 14 did not attend follow-up echocardiogram, 3 were excluded due to poor quality of echocardiographic images and 7 were retrospectively excluded because of a loss of blood samples (Fig. 1). A total of 68 patients with complete biological data and both initial and follow-up echocardiography was included in the analysis. Baseline characteristics

are depicted in Table 1. Median age was  $58.5 \pm 12.8$  years and 56 (82.4%) were men. Baseline LVEF was  $45.0 \pm 8.5\%$  (Table 2). Drug therapy at baseline and at follow-up is depicted in Table 3. The mean follow-up time was 7 months [6 to 10 months].

As shown in Table 1, baseline characteristics were comparable between groups (low-level of neprilysin group [ $\leq 125$  pg/mL,  $n = 38$ ], medium-level of neprilysin group [126–450 pg/mL,  $n = 15$ ] and a high-level group [ $> 450$  pg/mL,  $n = 15$ ]). Similarly, as shown in Table 2, baseline NT-proBNP levels and hs-cTnI levels were similarly distributed between groups with no correlation between the levels of the two latter and neprilysin levels ( $r = 0.06$  and  $r = 0.08$ , respectively). The relationship between neprilysin levels and the changes of LV volumes between baseline and follow-up is depicted in Fig. 2. There were no significant correlation between levels of NT-proBNP, hs-cTnI or neprilysin and the EDV change between baseline and follow-up ( $r = 0.07$ ,  $r = 0.09$  and  $r = 0.07$ , respectively). At baseline there was a non-significant trend towards lower EDV but significantly lower LVEF in the high neprilysin group ( $p = 0.07$  and  $p < 0.01$ , respectively, vs. other groups, Table 2 and Figs. 3 and 4). During follow-up, LVEF increased in both low and the high neprilysin level groups ( $46.4 \pm 8.3\%$  to  $53.0 \pm 8.9\%$ ,  $p < 0.001$ ; and  $39.1 \pm 6.9\%$  to  $50.4 \pm 9.9\%$ ,  $p < 0.001$  respectively). The magnitude of LVEF increase during follow-up was significantly more important in the high neprilysin group compared to the other groups ( $p = 0.022$  for relative and  $p = 0.031$  for absolute change in



**Fig. 1** Flow chart

**Table 1** Baseline characteristics according to neprilysin levels

|                                    | Overall (n = 68)  | Neprilysin level<br>≤ 125 pg/mL (n = 38) | Neprilysin level<br>126–450 pg/mL (n = 15) | Neprilysin level<br>> 450 pg/mL (n = 15) | Overall<br>p.value | Highest-level vs.<br>lower groups p.value |
|------------------------------------|-------------------|------------------------------------------|--------------------------------------------|------------------------------------------|--------------------|-------------------------------------------|
| Age, years                         | 58.5 ± 12.8       | 59.8 ± 11.7                              | 54.8 ± 9.8                                 | 60.5 ± 16.8                              | 0.37               | 0.58                                      |
| Gender, male                       | 56 (82.4%)        | 31 (81.6%)                               | 13 (86.7%)                                 | 12 (80.0%)                               | 0.88               | 1                                         |
| Hypertension                       | 25 (36.8%)        | 11 (28.9%)                               | 6 (40.0%)                                  | 8 (53.3%)                                | 0.25               | 0.23                                      |
| Diabetes mellitus                  | 13 (19.1%)        | 7 (18.4%)                                | 3 (20.0%)                                  | 3 (20.0%)                                | 0.99               | 1                                         |
| Hypercholesterolemia               | 33 (48.5%)        | 19 (50.0%)                               | 6 (40.0%)                                  | 8 (53.3%)                                | 0.74               | 0.90                                      |
| Current smoking                    | 43 (63.2%)        | 26 (68.4%)                               | 8 (53.3%)                                  | 9 (60.0%)                                | 0.57               | 1                                         |
| Body Mass Index, kg/m <sup>2</sup> | 26.1 [24.0, 29.4] | 26.0 [23.6, 29.3]                        | 28.5 [26.3, 29.3]                          | 25.8 [23.4, 30.0]                        | 0.45               | 0.75                                      |
| Heart rate, bpm                    | 77 ± 17           | 75 ± 15                                  | 80 ± 19                                    | 78 ± 20                                  | 0.62               | 0.77                                      |
| Systolic BP, mmHg                  | 142 ± 25          | 145 ± 28                                 | 134 ± 22                                   | 145 ± 22                                 | 0.39               | 0.65                                      |
| Diastolic BP, mmHg                 | 85 ± 19           | 87 ± 16                                  | 78 ± 21                                    | 86 ± 22                                  | 0.26               | 0.83                                      |
| Anterior STEMI                     | 27 (39.7%)        | 15 (39.5%)                               | 6 (40.0%)                                  | 6 (40.0%)                                | 1                  | 1                                         |
| Symptoms to balloon, hours         | 4.7 [3.1, 8.7]    | 4.5 [3.2, 6.0]                           | 3.7 [2.7, 8.6]                             | 6.8 [3.9, 10.8]                          | 0.36               | 0.18                                      |
| Thrombolysis                       | 2 (2.9%)          | 1 (2.6%)                                 | 0                                          | 1 (6.7%)                                 | 0.69               | 0.40                                      |
| GFR, mL/min/1.73m <sup>2</sup>     | 93 ± 17           | 91 ± 16                                  | 96 ± 19                                    | 93 ± 16                                  | 0.65               | 0.88                                      |

BP blood pressure, GFR glomerular filtration rate, STEMI ST-elevation myocardial infarction

LVEF, Table 2) resulting in similar LVEF levels at follow-up between all groups. Neprilysin values were independently associated with an improvement of LVEF during follow-up in multivariate analysis (Table 4). There was no ischemic event during follow-up. Six patients underwent planned coronary revascularization after the index hospitalization.

### Discussion

The present study is the first to show that after admission for STEMI highest levels of plasma neprilysin are associated with lower LVEF and a trend towards lower EDV at baseline, and higher magnitude of improvement of LVEF at follow-up when compared to other groups. These findings suggest that high neprilysin levels may

**Table 2** Biological and echocardiographic data according to neprilysin levels. \*\*\**p* < 0.001 vs. baseline

|                         | Overall (n = 68)    | Neprilysin level<br>≤ 125 pg/mL (n = 38) | Neprilysin level<br>126–450 pg/mL (n = 15) | Neprilysin level<br>> 450 pg/mL (n = 15) | Overall<br>p.value | Highest-level vs. lower<br>groups p.value |
|-------------------------|---------------------|------------------------------------------|--------------------------------------------|------------------------------------------|--------------------|-------------------------------------------|
| At baseline             |                     |                                          |                                            |                                          |                    |                                           |
| NT-proBNP, pg/mL        | 187 [64, 790]       | 184 [66, 1155]                           | 287 [87, 566]                              | 217 [65, 1103]                           | 0.77               | 0.47                                      |
| hs-cTnI, pg/mL          | 1947 [159, 9948]    | 1511 [156, 9794]                         | 1136 [327, 6711]                           | 2765 [574, 10,492]                       | 0.64               | 0.38                                      |
| Neprilysin, pg/mL       | 125 [125, 432]      | –                                        | 350 [183, 411]                             | 1070 [781, 1824]                         |                    |                                           |
| At baseline             |                     |                                          |                                            |                                          |                    |                                           |
| EDV, mL/m <sup>2</sup>  | 53.8 ± 13.0         | 55.1 ± 12.4                              | 56.0 ± 13.5                                | 48.3 ± 13.3                              | 0.18               | 0.07                                      |
| ESV, mL/m <sup>2</sup>  | 28.2 [22.4, 34.7]   | 27.8 [23.2, 34.9]                        | 28.8 [24.3, 32.8]                          | 28.5 [21.1, 36.0]                        | 0.97               | 0.82                                      |
| LVEF, %                 | 45.0 ± 8.5          | 46.4 ± 8.3                               | 47.1 ± 8.1                                 | 39.1 ± 6.9                               | < 0.01             | < 0.01                                    |
| At follow-up            |                     |                                          |                                            |                                          |                    |                                           |
| EDV, mL/m <sup>2</sup>  | 56.6 ± 15.0         | 57.8 ± 13.6                              | 58.7 ± 19.9                                | 51.6 ± 12.6                              | 0.35               | 0.15                                      |
| %increase in EDV        | 4.6 [−8.6, 18.6]    | −0.1 [8.9, 17.4]                         | 5.9 [−11.4, 22.1]                          | 10.7 [−5.3, 20.5]                        | 0.69               | 0.39                                      |
| ΔEDV, mL/m <sup>2</sup> | 5.4 ± 23.2          | 5.5 ± 22.7                               | 5.4 ± 28.6                                 | 5.1 ± 20.0                               | 1                  | 0.96                                      |
| ESV, mL/m <sup>2</sup>  | 25.4 [19.0, 34.8]   | 25.8 [19.6, 32.7]                        | 25.9 [18.9, 36.5]                          | 25.1 [19.1, 32.3]                        | 0.91               | 0.66                                      |
| %increase in ESV        | −14.3 [−23.3, 10.5] | −10.9 [−22.1, 9.7]                       | −11.1 [−27.0, 28.8]                        | −15.2 [−24.2, 1.6]                       | 0.69               | 0.44                                      |
| ΔESV, mL/m <sup>2</sup> | −4.2 ± 17.7         | −3.7 ± 17.3                              | −0.8 ± 20.9                                | −8.9 ± 15.4                              | 0.46               | 0.26                                      |
| LVEF, %                 | 51.9 ± 9.2***       | 53.0 ± 8.9***                            | 50.6 ± 9.7                                 | 50.4 ± 9.9***                            | 0.55               | 0.49                                      |
| %increase in LVEF       | 17.7 ± 22.0         | 16.0 ± 19.4                              | 9.1 ± 21.5                                 | 30.3 ± 24.5                              | 0.022              | 0.01                                      |
| ΔLVEF, %                | 7.0 ± 8.3           | 6.6 ± 7.3                                | 3.6 ± 9.0                                  | 11.3 ± 8.4                               | 0.031              | 0.02                                      |

EDV end-diastolic volume, ESV end-systolic volume, hs-cTnI high-sensitivity cardiac troponin I, LVEF left ventricular ejection fraction

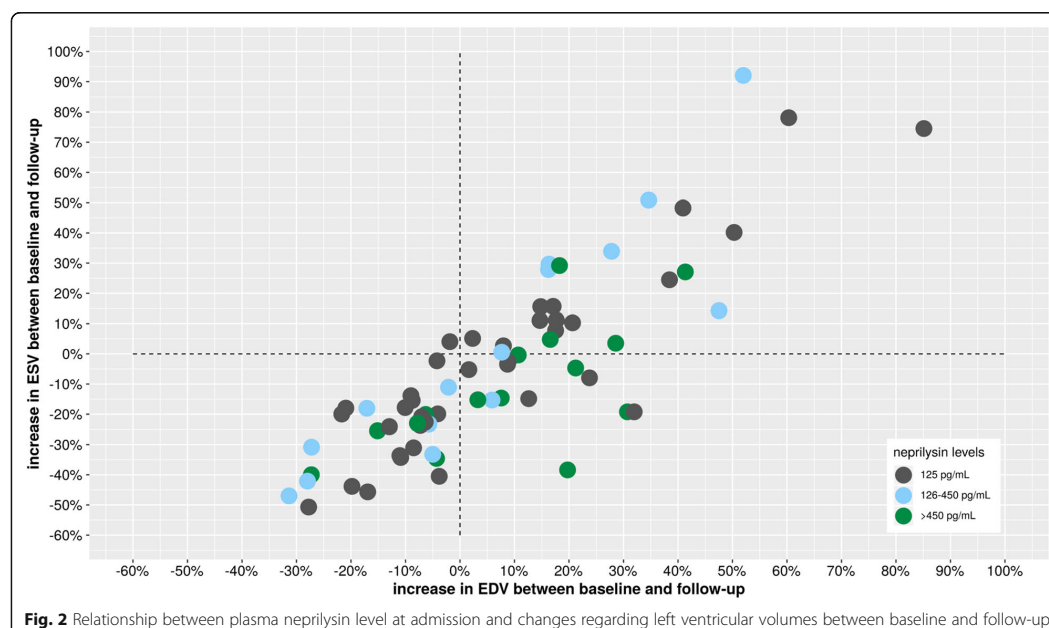
**Table 3** Drug therapy according to neprilysin levels, at baseline and at follow-up

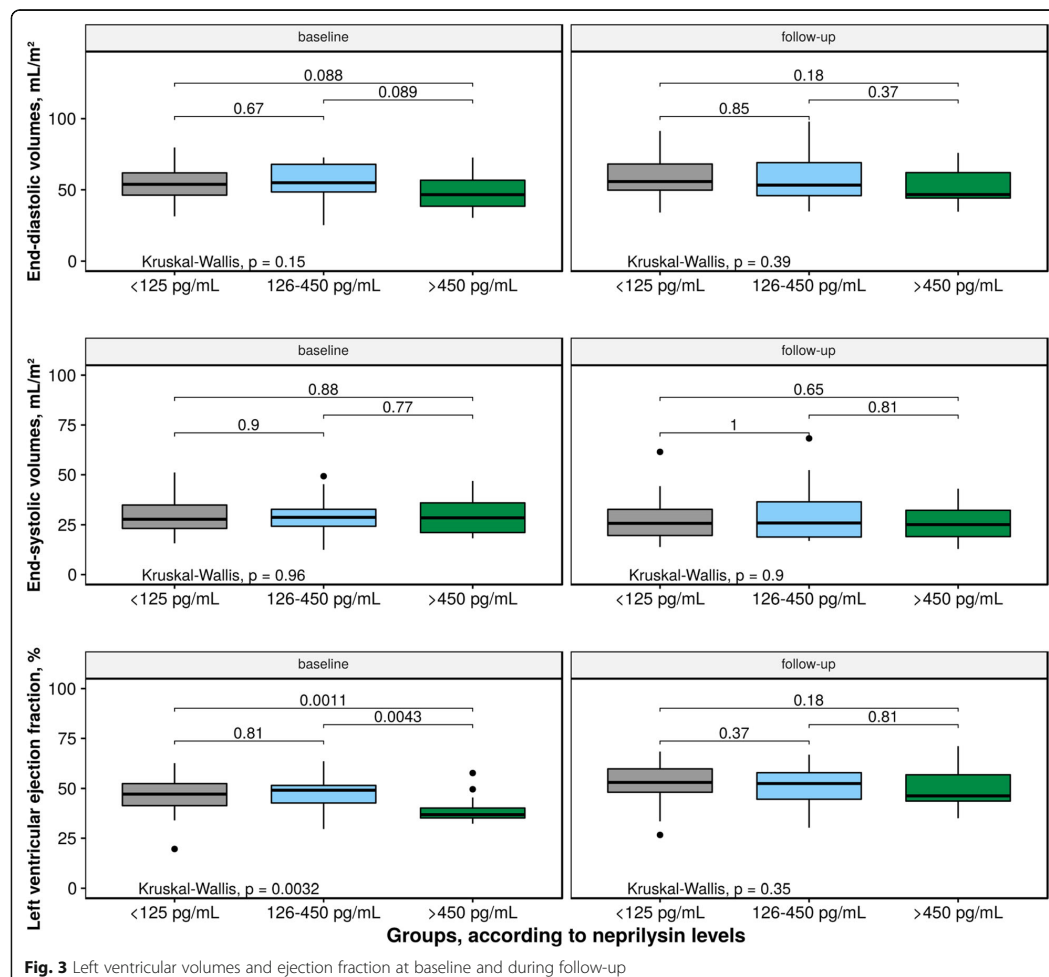
|                    | Overall (n = 68) | Neprilysin level<br>≤ 125 pg/mL (n = 38) | Neprilysin level<br>126–450 pg/mL (n = 15) | Neprilysin level<br>> 450 pg/mL (n = 15) | Overall p.value | Highest-level vs.<br>lower groups p.value |
|--------------------|------------------|------------------------------------------|--------------------------------------------|------------------------------------------|-----------------|-------------------------------------------|
| At baseline        |                  |                                          |                                            |                                          |                 |                                           |
| antiplatelet agent | 6 (8.8%)         | 2 (5.3%)                                 | 1 (6.7%)                                   | 3 (20.0%)                                | 0.23            | 0.23                                      |
| beta-blocker       | 3 (4.4%)         | 2 (5.3%)                                 | 0                                          | 1 (6.7%)                                 | 0.63            | 1                                         |
| ACEI/ARB/MRA       | 18 (26.5%)       | 8 (21.1%)                                | 5 (33.3%)                                  | 5 (33.3%)                                | 0.53            | 0.73                                      |
| statins            | 17 (25.0%)       | 9 (23.7%)                                | 4 (26.7%)                                  | 4 (26.7%)                                | 0.97            | 1                                         |
| diuretics          | 7 (10.3%)        | 3 (7.9%)                                 | 2 (13.3%)                                  | 2 (13.3%)                                | 0.77            | 1                                         |
| At follow-up       |                  |                                          |                                            |                                          |                 |                                           |
| antiplatelet agent | 68 (100.0%)      | 38 (100.0%)                              | 15 (100.0%)                                | 15 (100.0%)                              | –               |                                           |
| beta-blocker       | 64 (94.1%)       | 36 (94.7%)                               | 14 (93.3%)                                 | 14 (93.3%)                               | 0.98            | 1                                         |
| ACEI/ARB/MRA       | 52 (76.5%)       | 30 (78.9%)                               | 12 (80.0%)                                 | 10 (66.7%)                               | 0.60            | 0.51                                      |
| statins            | 65 (95.6%)       | 37 (97.4%)                               | 15 (100.0%)                                | 13 (86.7%)                               | 0.15            | 0.24                                      |
| diuretics          | 11 (16.2%)       | 7 (18.4%)                                | 2 (13.3%)                                  | 2 (13.3%)                                | 0.86            | 1                                         |

identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up.

Neprilysin is a neutral endopeptidase that degrades several endogenous vasoactive peptides, such as natriuretic peptides, Angiotensin-II, Endothelin-1, bradykinin, substance P and adrenomedullin [9, 10] which may be involved in the post STEMI neurohormonal activation. More than half of the patients (55.9%) had a very low levels of neprilysin at baseline, below the measurement threshold of 125 pg/mL in the present study. Serial

measurements of serum neprilysin concentration following STEMI in a prior study have shown comparable results to our study with a median initial neprilysin level of 88.3 pg/mL [IQR: 14, 375.5] [14]. Low levels of neprilysin have been reported to be associated with cardiovascular risk factors such as hypertension and smoking as well as diastolic left ventricular dysfunction in a large community-based cohort of 1536 participants without known cardiovascular disease (median of 3.9 ng/mL [IQR: 1.0, 43.0 ng/mL] [15]). The latter two studies failed to show an impact of neprilysin levels on outcome. These

**Fig. 2** Relationship between plasma neprilysin level at admission and changes regarding left ventricular volumes between baseline and follow-up



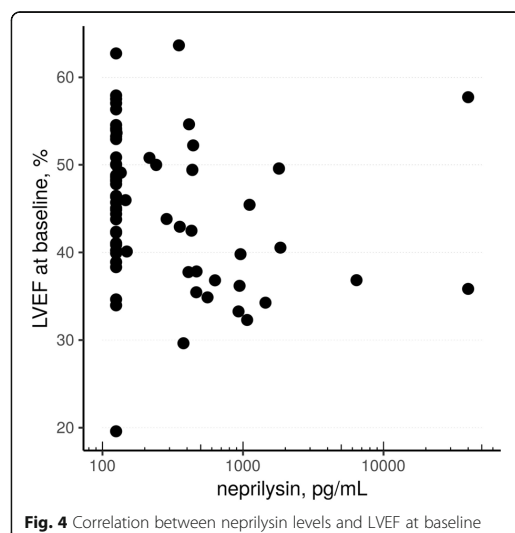
**Fig. 3** Left ventricular volumes and ejection fraction at baseline and during follow-up

data support a complex relationship between neprilysin levels and cardiac functional or structural compromise in possibly different directions in different conditions. Such complex relationship is not paradoxical as neprilysin degrades effectors with opposite effects. Its action, up- or down-regulation, and maybe inhibition may therefore lead potentially to either beneficial or detrimental effects.

After STEMI, early neurohormonal activation occurs in order to maintain hemodynamic homeostasis [16]. Our study was limited to patients without HF or severely reduced LVEF. We found a mild increase in natriuretic peptides levels and mildly reduced LVEF in the study population. Neprilysin catalyzes the degradation of several vasodilator peptides, especially natriuretic peptides but also bradykinin, substance P, and adrenomedullin [17]. It

is likely that the increase of the level of these peptides is at least partly related to a decrease of plasma neprilysin concentrations although the direction of such relationship could not be identified. In the above mentioned large community-based cohort, excluding patients with a LVEF < 45%, low neprilysin levels were associated with higher prevalence of smokers, hypertension, dyslipidemia and impaired diastolic function [15]). Although the level of plasma neprilysin were not available before the onset of STEMI in our study, it may be speculated that most patients included in our analysis, with cardiovascular risk factors, may have had low levels of neprilysin prior to acute myocardial infarction.

The associations between low soluble neprilysin levels and an adverse cardiometabolic and smoking profile in



the general population on one hand and the association between high levels and poor outcome [18–20] as well as the beneficial effect of simultaneous neprilysin and angiotensinII inhibition in HF with altered LVEF populations [12] may be explained by different populations and different levels and patterns of neurohormonal activation. Endothelial dysfunction and the subsequent vasoconstriction, are common findings in patients with coronary artery disease risk factors (hypertension,

smoking, dyslipidemia) [21]. Neprilysin degrades atrial natriuretic peptide which is a key signaling pathway in blood pressure regulation [22]. The association between such risk factors and the lower levels of neprilysin in the general population may be explained by the down-regulation of neprilysin in this setting to counteract impaired vasomotion, while in the setting of HF, high levels of neprilysin, upregulated by the increase of natriuretic peptides levels, are associated with detrimental effects which may be prevented by its inhibition [12].

The present STEMI population is different from both the general population and the chronic or acute HF patient populations. Hemodynamic status and the evolution of cardiac volumes and function are obviously different between patients without cardiovascular disease, with subclinical diastolic LV dysfunction, HF with preserved or decreased LVEF and finally the acute ischemic injury and LV overload of STEMI. The impact of neurohormonal activation after STEMI on cardiac remodeling increases as the reparative and proliferative phases begin. The post STEMI left ventricular overload leads to increased proBNP production by left ventricular cardiomyocytes [23]. Neprilysin clears BNP from circulation, resulting in a limitation of its adaptive natriuretic action [22]. There are controversial data about the ability of natriuretic peptides levels at admission to predict LVR following STEMI [24–26]. Our study, in concordance with prior studies, showed that soluble neprilysin levels were not correlated to natriuretic peptide levels [15] at the time of measurement, early after STEMI. Accordingly, we observed no correlation between initial assessment of neprilysin levels and adverse remodeling

**Table 4** LVEF improvement at follow-up: univariate and multivariate analysis

|                      | Correlation coefficient, [95%CI] | Univariate p-value | Multivariate beta coefficient, [95%CI] | Multivariate p-value |
|----------------------|----------------------------------|--------------------|----------------------------------------|----------------------|
| Age                  | −0.04 [−0.20, 0.12]              | 0.63               |                                        |                      |
| Gender, male         | 0.97 [−4.30, 6.24]               | 0.71               |                                        |                      |
| Hypertension         | −0.16 [−4.34, 4.01]              | 0.94               |                                        |                      |
| Diabetes mellitus    | 2.50 [−2.58, 7.59]               | 0.33               |                                        |                      |
| Hypercholesterolemia | 2.77 [−1.20, 6.74]               | 0.17               |                                        |                      |
| Current smoking      | −3.90 [−7.95, 0.17]              | 0.06               | −3.41 [−7.35, 0.53]                    | 0.09                 |
| Body Mass Index,     | 0.14 [−0.30, 0.58]               | 0.52               |                                        |                      |
| Heart rate           | 0.13 [0.02, 0.24]                | 0.03               | 0.09 [−0.03, 0.20]                     | 0.13                 |
| Systolic BP          | 0.04 [−0.04, 0.12]               | 0.30               |                                        |                      |
| Diastolic BP         | −0.03 [−0.14, 0.08]              | 0.57               |                                        |                      |
| Anterior STEMI       | 1.79 [−2.30, 5.88]               | 0.38               |                                        |                      |
| Symptoms to balloon  | −0.17 [−0.55, 0.20]              | 0.36               |                                        |                      |
| GFR                  | 0.06 [−0.07, 0.19]               | 0.36               |                                        |                      |
| log neprilysin       | 1.85 [0.31, 3.40]                | 0.02               | 1.62 [0.13, 3.11]                      | 0.03                 |
| log NT-proBNP        | −0.98 [−2.17, 0.22]              | 0.11               | −0.99 [−2.12, 0.13]                    | 0.08                 |
| log hs-cTnI          | −0.43 [−1.26, 0.40]              | 0.30               |                                        |                      |

during follow-up. These results, in concordance with a prior study [14] suggest that neprilysin may not be an early biomarker of adverse remodeling after STEMI. Unlike the prior study, we assessed dynamic changes of LV volumes and function. The lower LVEF observed in STEMI patients with the highest levels of neprilysin in our study was driven by a non-significant lower EDV at baseline. Interestingly, these patients showed significant improvement of LVEF at follow-up when compared to other groups. These findings arise the hypothesis of a relationship between high levels of neprilysin and the extent of stunned myocardium, with low contractility at baseline and recovery at follow-up following successful myocardial reperfusion. One speculative explanation to our findings may be that in patients with extended stunned myocardium, levels of BNP may be high very early after STEMI, leading to an up-regulation of neprilysin, leading itself to a reduction of BNP levels at the time of measurement. In such patients without LV enlargement and heart failure higher levels of neprilysin may only be a marker of stunned myocardium, recovering at follow-up. Other hypotheses with a beneficial action of high levels of neprilysin, as a direct or indirect consequence of post-STEMI neurohormonal activation, acting more effectively on vasoconstrictive/pro-proliferative peptides may be considered. Bernelin et al. showed a non-significant decrease of neprilysin levels following STEMI, from baseline, to 1 month [14]. This non-significant trend ( $p = 0.70$ ) may possibly be related to the small sample size ( $n = 21$ ) in the latter study. The latter study evaluated LV volumes and function only once at 1 month, hence not allowing the analysis of changes in such parameters. In our study neprilysin level measurements were performed only once, on admission, hence not allowing any analysis of the impact of neprilysin level kinetics on the studied parameters. It may be interesting to assess the evolution of neprilysin concentrations and the evolution of cardiac imaging parameters in a larger STEMI population at different timepoints.

The present study has several limitations. The analysis includes a small number of patients. The population is highly selected including only patients with successful myocardial reperfusion, without heart failure and who had complete 3D-transthoracic echocardiogram at 2 time-points and a collection of blood samples. Because of a high drop-out rate a selection bias could not be excluded. Our results could not be generalized to all settings of STEMI. Neprilysin has complex pleiotropic effects and is involved in different pathways and our study may not assess the pathophysiological bases of our findings. Moreover, the absence of correlation between circulating neprilysin concentration and activity has been previously reported [27].

## Conclusions

Our study shows that after admission for STEMI, in a selected population with successful myocardial reperfusion and no clinical sign of HF, highest levels of plasma neprilysin are associated with lower LVEF at baseline, a trend towards lower EDV and higher magnitude of improvement of LVEF at follow-up when compared to other groups. These findings suggest that high neprilysin levels may identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up. If confirmed by other large sized studies, neprilysin level measurements may contribute to identifying patients with decreased LVEF at baseline but who are more likely to recover at follow-up. Further studies are also warranted to assess the impact of neprilysin in the general setting of STEMI and its potential blockade.

## Abbreviations

ACE: Angiotensin-converting enzyme; AT1: Angiotensin-II receptor type 1; BNP: Brain natriuretic peptide; EDV: End-diastolic volume; ESV: End-systolic volume; HF: Heart failure; hs-cTnI: High-sensitivity cardiac troponin I; LV: Left ventricular; LVEF: Left ventricular ejection fraction; LVR: Left ventricular remodeling; NTpro-BNP: N-terminal pro-B-type natriuretic peptide; pPCI: Primary percutaneous coronary intervention; RAAS: Renin-angiotensin-aldosterone system; STEMI: ST-elevation myocardial infarction

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## Authors' contributions

DL extracted and analyzed the data and drafted the manuscript. CM extracted the data and drafted the manuscript. AH and ES carried out echocardiography imaging and revised the manuscript. SA performed the assays and revised the manuscript. IEK extracted the data. AM revised the manuscript. PM participated in data analysis and revised the manuscript. FB designed the study, analysed the data and revised the manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

Written informed consent was obtained from the patients. This non-interventional study complied with the Declaration of Helsinki and was approved by the local ethics committee (Comité de Protection des Personnes Nord-Ouest 3, Centre Hospitalier Universitaire de Caen, France). The protocol registration number is A14-D17-VOL20.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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## References

- Huttin O, Coiro S, Seltou-Suty C, Juillière Y, Donal E, Magne J, Sadoul N, Zannad F, Rossignol P, Girerd N. Prediction of left ventricular remodeling after a myocardial infarction: role of myocardial deformation: a systematic review and meta-analysis. *PLoS One*. 2016;11:e0168349.
- Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, ESC Scientific Document Group. 2018 ESC/EAACS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165.
- St John Sutton M, Lee D, Rouleau JL, Goldman S, Plappert T, Braunwald E, Pfeffer MA. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. *Circulation*. 2003;107:2577–82.
- Dorn GW 2nd. Novel pharmacotherapies to abrogate postinfarction ventricular remodeling. *Nat Rev Cardiol*. 2009;6:283–91.
- Palardy M, Ducharme A, O'Meara E. Inhibiting the renin-angiotensin system with ACE inhibitors or ARBs after MI. *Curr Heart Fail Rep*. 2007;4:190–7.
- Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation*. 1998;97:2202–2212.
- Solomon SD, Skali H, Anavekar NS, Bourgoin M, Barvik S, Ghali JK, Wamala JW, Khrakovskaya M, Arnold JM, Schwartz Y, Velazquez EJ, Califf RM, McMurray JJ, Pfeffer MA. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. *Circulation*. 2005;111:3411–9.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Vahrenhorst C, Vranckx P, Widimský P, ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–77.
- Cruden NL, Fox KA, Ludlam CA, Johnston NR, Newby DE. Neutral endopeptidase inhibition augments vascular actions of bradykinin in patients treated with angiotensin-converting enzyme inhibition. *Hypertension*. 2004;44:913–8.
- Wilkinson IB, McEniery CM, Bongaerts KH, MacCallum H, Webb DJ, Cockcroft JR. Adrenomedullin (ADM) in the human forearm vascular bed: effect of neutral endopeptidase inhibition and comparison with adrenomedullin NH2-terminal 20 peptide (PAMP). *Br J Clin Pharmacol*. 2001;52:159–64.
- Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNI). *J Clin Pharmacol*. 2010;50:401–14.
- McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
- Martens P, Belien H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovasc Ther*. 2018;36:e12435.
- Bernelin H, Mewton N, Si-Mohamed S, Croisille P, Rioufol G, Bonnefoy-Cudraz E, Douek P, Dufay N, Amaz C, Jossan C, Ovize M, Bochaton T. Neprilysin levels at the acute phase of ST-elevation myocardial infarction. *Clin Cardiol*. 2019;42:32–8.
- Reddy YNV, Iyer SR, Scott CG, Rodeheffer RJ, Bailey K, Jenkins G, Batzler A, Redfield MM, Burnett JC Jr, Pereira NL. Soluble neprilysin in the general population: clinical determinants and its relationship to cardiovascular disease. *J Am Heart Assoc*. 2019;8:e012943.
- Bacmeister L, Schwarzl M, Warnke S, Stoffers B, Blankenberg S, Westermann D, Lindner D. Inflammation and fibrosis in murine models of heart failure. *Basic Res Cardiol*. 2019;114:19.
- Vardeny O, Tacheny T, Solomon SD. First-in-class angiotensin receptor neprilysin inhibitor in heart failure. *Clin Pharmacol Ther*. 2013;94:445–8.
- Bayés-Genís A, Barallat J, Galán A, de Antonio M, Domingo M, Zamora E, Urrutia A, Lupón J. Soluble neprilysin is predictive of cardiovascular death and heart failure hospitalization in heart failure patients. *J Am Coll Cardiol*. 2015;65:657–65.
- Bayés-Genís A, Barallat J, Pascual-Figal D, Nuñez J, Miñana G, Sánchez-Mas J, Galán A, Sanchis J, Zamora E, Pérez-Martínez MT, Lupón J. Prognostic value and kinetics of soluble neprilysin in acute heart failure. *JACC Heart Fail*. 2015;3:641–4.
- Núñez J, Núñez E, Barallat J, Bodí V, Miñana G, Pastor MC, Sanchis J, Lupón J, Bayes-Genís A. Serum neprilysin and recurrent admissions in patients with heart failure. *J Am Heart Assoc*. 2017;6:e005712.
- Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, Schoene N, Schuler G. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med*. 2000;342:454–60.
- Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. *Handb Exp Pharmacol*. 2009;191:341–66.
- Lippi G, Sanchis-Gomar F. Monitoring b-type natriuretic peptide in patients undergoing therapy with neprilysin inhibitors. An emerging challenge? *Int J Cardiol*. 2016;219:111–4.
- Hole T, Hall C, Skærpe T. N-terminal proatrial natriuretic peptide predicts two-year remodelling in patients with acute transmural myocardial infarction. *Eur Heart J*. 2004;25:416–23.
- Manhenke C, Ueland T, Jugdutt BI, Godang K, Aukrust P, Dickstein K, Ørn S. The relationship between markers of extracellular cardiac matrix turnover: infarct healing and left ventricular remodelling following primary PCI in patients with first-time STEMI. *Eur Heart J*. 2014;35:395–402.
- Urbano-Moral JA, Lopez-Haldon JE, Fernandez M, Mancha F, Sanchez A, Rodriguez-Puras MJ, Villa M, Lopez-Pardo F, Diaz de la Llera L, Valle JL, Martinez A. Prognostic value of different serum biomarkers for left ventricular remodelling after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. 2012;98:1153–9.
- Vodovar N, Séronde MF, Laribi S, Gayat E, Lassus J, Januzzi JL Jr, Boukef R, Nouira S, Manivet P, Samuel JL, Logeart D, Cohen-Solal A, Richards AM, Launay JM, Mebazaa A, Network GREAT. Elevated plasma B-type natriuretic peptide concentrations directly inhibit circulating Neprilysin activity in heart failure. *JACC Heart Fail*. 2015;3:629–36.

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## **Relation entre taux de coenzyme Q10 et remodelage ventriculaire gauche**

Lors de la revascularisation coronaire, il existe paradoxalement des lésions myocardiques secondaires à la restauration du flux sanguin [110]. Il a été précédemment montré que ces lésions d'ischémie-reperfusion sont responsables d'une partie significative de la taille finale de l'infarctus [111, 112]. Par ailleurs, l'ischémie-reperfusion induit un dysfonctionnement de la fonction mitochondriale conduisant à la production d'ERO avec pour conséquence la survenue de dégâts cellulaires par peroxydation des lipides, déséquilibre de la balance entre les agents antioxydants et oxydants et finalement, diminution globale de la capacité à produire de l'énergie à l'étage mitochondrial [113]. Nous nous sommes donc intéressés au rôle du coenzyme Q10 (CoQ10) (ou ubiquinone/ubiquinol), vitamine liposoluble majoritairement localisée dans la paroi interne des mitochondries [114] et dont les effets biologiques sont multiples: transport d'électrons entre les complexes de la chaîne respiratoire mitochondriale [115], antioxydant [116], phosphorylation de diverses structures extra-mitochondriales, régulation de la perméabilité du pore de transition mitochondrial ou encore amélioration de la dysfonction endothéliale, probablement par stimulation de la synthèse de NO [117].

Nous avons dosé le CoQ10 chez 68 patients de notre registre RESIST pour lesquels nous disposions de données échocardiographiques complètes, à la phase initiale et au cours du suivi, mais aussi de prélèvements sanguins prélevés sur tubes EDTA, au moment de la procédure de revascularisation coronaire. Les patients ont été séparés en deux groupes selon l'existence ou non d'un RVG défini comme une augmentation d'au moins 20% du volume télédiastolique entre les deux sessions d'imagerie. Dans ce travail, nous n'avons pas trouvé

d'association entre les taux sériques de CoQ10 à la phase aiguë du STEMI et le RVG au cours du suivi ( $1,20 \mu\text{mol/L} \pm 0,42 \mu\text{mol/L}$  dans le groupe remodelage vs.  $1,23 \mu\text{mol/L} \pm 0,32 \mu\text{mol/L}$  dans le groupe sans remodelage ;  $p=0.78$ ).

Fontaine F, **Legallois D**, Creveuil C, Chtouri M, Coulbault L, Hodzic A, Saloux E, Milliez P, Beygui F, Allouche S.

Is plasma level of Coenzyme Q10 a predictive marker for left ventricular remodeling after revascularization for ST-segment elevation myocardial infarction ?

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## Is plasma level of Coenzyme Q10 a predictive marker for left ventricular remodeling after revascularization for ST-segment elevation myocardial infarction ?

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### ABSTRACT

**Background.** Left ventricular remodeling (LVR) that frequently occurs after acute myocardial infarction (AMI) is associated with an increased risk of heart failure and cardiovascular death. Although several risk factors have been identified, there is still no marker in clinical use to predict LVR. Plasma level of Coenzyme Q10 (CoQ10), that plays a key role in mitochondrial energy production and as an antioxidant, was shown to be negatively correlated with mortality after AMI.

**Objective.** The goal of our study was to determine whether the plasma CoQ10 baseline concentration at time of the ST-elevation myocardial infarction (STEMI) could predict the LVR at 6 months of follow-up.

**Methods.** 68 patients who were admitted to hospital for STEMI and successfully revascularized with primary percutaneous coronary intervention (PPCI) were recruited. All patients underwent a 3D-echocardiography examination within the first 4 days after PPCI and 6 months later and were divided into a favorable and an unfavorable LVR groups. Plasma CoQ10 level at the time of PPCI was determined using high performance liquid chromatography-tandem mass spectrometry (HPLC/MSMS).

**Results.** While we found similar plasma CoQ10 concentrations compared to other studies, no statistical difference was evidenced between unfavorable or favorable remodeling groups (RR=0.99 ; 95%CI[0.90 ; 1.09] ; p=0.89).

**Conclusion.** We found no evidence for using plasma CoQ10 concentration as an early prediction marker for LVR after STEMI.

**ABBREVIATIONS**

|            |                                                                 |
|------------|-----------------------------------------------------------------|
| AMI        | Acute myocardial infarction                                     |
| BMI        | Body Mass Index                                                 |
| CoQ10      | Coenzyme Q10                                                    |
| ECG        | Electrocardiogram                                               |
| EDV        | End-diastolic volume                                            |
| ESV        | End-systolic volume                                             |
| HF         | Heart failure                                                   |
| HPLC/MSMS  | High performance liquid chromatography-tandem mass spectrometry |
| hs-TnI     | High-sensibility cardiac troponin I                             |
| LV         | Left ventricular                                                |
| LVEF       | Left ventricular ejection fraction                              |
| LVR        | Left ventricular remodeling                                     |
| NT-pro-BNP | N-terminal pro-B-type natriuretic peptide                       |
| PPCI       | Primary percutaneous coronary intervention                      |
| ROS        | Reactive oxygen species                                         |
| STEMI      | ST-elevation myocardial infarction                              |
| TIMI       | Thrombolysis in myocardial infarction                           |

## INTRODUCTION

Acute myocardial infarction (AMI) is a common and severe disease, and constitutes a great socioeconomic burden for society, with high mortality and morbidity.<sup>1</sup> Over the past few decades, reperfusion therapies and secondary prevention medications have considerably reduced short-term mortality after AMI. Paradoxically, patients who survive are more likely to develop left ventricular remodeling (LVR), a progressive alteration in ventricular function and architecture that ultimately results in an increased risk of heart failure (HF) and cardiovascular death.<sup>2,3</sup> Morphological changes include cardiomyocyte loss, cardiac hypertrophy and fibrosis.<sup>4</sup> Several molecules have been investigated for LVR prediction, including natriuretic peptides, markers of fibrosis (collagen peptides, matrix metalloproteinases) and markers of inflammation (Soluble suppression of tumorigenicity 2 or SST2, Galectin-3).<sup>5</sup> However, there is still no reliable biomarker that could be used in clinical practice for early diagnosis and management of patients undergoing LVR.<sup>6</sup> This is probably due to the complexity of the pathophysiological mechanisms involved in LVR which is a dynamic, time-dependent and multifactorial process triggered by mechanical stretch, neurohormonal activation, inflammation, metabolic abnormalities and oxidative stress.<sup>7</sup> It is well admitted that mitochondrial dysfunction which results from ischemia/reperfusion injury leads to reactive oxygen species (ROS)-induced cellular damages, including lipid peroxidation, antioxidant deficiency and decrease in energy production.<sup>8,9</sup>

Coenzyme Q10 (CoQ10), or ubiquinone/ubiquinol, is a liposoluble vitamin-like molecule mainly located within the inner mitochondrial membrane.<sup>10</sup> CoQ10 plays a key role in oxidative phosphorylation, acting as an electron transporter from mitochondrial complexes I and II to complex III.<sup>11</sup> It also acts as a powerful endogenous antioxidant and free radical scavenger due to its ability to switch from a reduced to an oxidized state (ubiquinol  $\rightleftharpoons$  semiquinone  $\rightleftharpoons$  ubiquinone).<sup>12</sup> Other biological functions of CoQ10 include extramitochondrial oxidative phosphorylation (platelets, myelin sheath, retina...), regulation of the mitochondrial permeability transition pore, activation of mitochondrial uncoupling proteins and improvement of endothelial dysfunction (probably by increasing nitrogen oxide).<sup>13</sup>

In rat models of AMI, pretreatment with exogenous administration of CoQ10 has been shown to reduce infarct size and preserve ventricular function by reducing oxidative stress, pro-inflammatory cytokines and pro-apoptotic factors.<sup>14,15,16</sup> A recent clinical study suggests that early CoQ10 supplementation in patients with left ventricular ejection fraction < 50% after AMI may reduce LVR.<sup>17</sup> In another study, plasma CoQ10 concentrations at 1 month after PPCI in patients with STEMI are positively correlated with favorable LVR.<sup>18</sup> These studies suggest that CoQ10 could play a key role in LVR, by reducing ROS production and optimizing mitochondrial function, but data are scarce and the clinical interest of CoQ10 level in AMI has to be established.<sup>19,20</sup>

Therefore, we hypothesized that a low plasma CoQ10 level at the time of myocardial infarction may be associated with an increased risk of developing adverse LVR at 6 months of follow-up.

## MATERIALS AND METHODS

### Patients and study protocol

A total of 68 adult patients admitted for STEMI and treated with PPCI between 2017 January 1<sup>st</sup> and 2018 October 30 at Caen University Hospital (France) were retrospectively enrolled. This study is an ancillary study to that designed by Legallois *et al.* and inclusion and exclusion criteria were as previously described.<sup>21</sup> The study complied with the Declaration of Helsinki and was approved by the local ethics committee (protocol number A14-D17-VOL.20).

A second and totally distinct cohort of patients was designed to compare plasma and muscle CoQ10 levels. We prospectively enrolled 12 patients who simultaneously underwent a muscle biopsy and a blood test in the course of the investigation of a putative mitochondrial disorder. Informed consent was obtained from all patients.

### Measurement of biochemical parameters

#### Plasma CoQ10 measurement

Peripheral venous blood samples for baseline plasma CoQ10 measurement were collected at the time of PPCI in Vacutainer tubes (Becton-Dickinson) with EDTA as anticoagulant. Samples were centrifuged at room temperature for 12 min at 2000g and plasma was stored at -80°C until analysis. The plasma CoQ10 concentration was determined using high performance liquid chromatography-tandem mass spectrometry (HPLC/MSMS) following a slightly modified procedure described by Ruiz-Jimenez *et al.*<sup>22</sup> A mixture of 100 µL of thawed plasma and 50 µL CoQ10-d<sup>9</sup> internal standard at 2 µg/mL was deproteinized with 500 µL methanol and extracted three times with 1000 µL *n*-hexane. The organic phases were pooled and evaporated to dryness using a vacuum concentrator. The dry residue was suspended within 100 µL of ethanol, vortexed for 2 min and put into vial. Three µL were injected on a NexeraXR® system (Shimadzu, Marne-la-Vallée, France) with a 3 µm (2,0 x 150mm) Pursuit PFP® column (Agilent, Santa Clara, USA). The mobile phase was methanol-formic acid 0.1% from 80:20 (v/v) to 100% methanol. The flow rate was fixed at 0.35 mL/min for 7.5 min and the temperature of the analytical column was 40°C. Detection and quantification were done by mass spectrometry using an API 5500 QTRAP® (ABSciex, Les Ulis, France) tandem mass spectrometer equipped with an APCI source in positive mode. CoQ10 was analyzed in the MRM mode with the following transitions: CoQ10 *m/z* 863.4 ± 197.1 and CoQ10-d<sup>9</sup> *m/z* 872.9 ± 206.3. Linearity was achieved over the following range:

0.02 to 2.30  $\mu\text{mol/L}$ . The intra- and inter-assay precision were respectively 3.3% and 6.6% for a CoQ10 concentration of 0.96  $\mu\text{mol/L}$  and 3.0% and 8.5% for a concentration of 1.97  $\mu\text{mol/L}$ . The recoveries of CoQ10 were comprised between 90 and 110%. Measurement of the patients' plasma CoQ10 level was performed in duplicate. Plasma CoQ10 concentration was expressed in  $\mu\text{mol/L}$  or indexed to LDL or total cholesterol ( $\mu\text{mol}/\text{mmol}$ ).

#### *Muscle CoQ10 measurement*

Muscle biopsies were stored at  $-80^{\circ}\text{C}$  until their preparation. Pieces of frozen tissue ( $m=30\text{--}50\text{mg}$ ) were homogenized twice in 10 volumes of grinding buffer (mannitol 225mM; sucrose 70mM; TRIS 10mM; EDTA 0,1mM; pH 7.2) using a tight-fit Potter-Elvehjem tissue grinder. Samples were centrifuged for 20 min at 650g at  $+4^{\circ}\text{C}$ . Supernatants were pooled and stored at  $-80^{\circ}\text{C}$  until CoQ10 quantification. CoQ10 concentration was determined as previously described using 40 $\mu\text{L}$  of the muscle homogenate diluted by a 2- or a 4-fold in grinding buffer (according to protein content), and 40 $\mu\text{L}$  of internal standard. Linearity was achieved over the following range: 0.015 to 2.30  $\mu\text{mol/L}$ . The intra-assay precision were respectively 3.92% for a CoQ10 concentration of 0.40  $\mu\text{mol/L}$  and 2.21% for a concentration of 0.74  $\mu\text{mol/L}$ . Protein content of muscle homogenate was determined with the bicinchoninic acid assay and muscle CoQ10 content was finally expressed as molar concentration per gram of protein (nmol/g of protein).<sup>23</sup>

#### *Other biochemical parameters*

Total cholesterol, high-density lipoprotein cholesterol and triglyceride concentrations were determined using an AU680 chemistry analyzer (Beckman Coulter). Plasma low-density lipoprotein cholesterol concentration was calculated using Friedwald equation when triglyceride level was over 3.75 mmol/L or determined using a Konelab 20 analyzer (Thermo Scientific). High sensitivity cardiac troponin I (hs-TnI) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) concentrations were respectively measured on a Unicel DxI system (Beckman Coulter) and a Cobas e411 system (Roche). Glomerular Flow Rate (GFR) was calculated using the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) equation.

#### **Echocardiographic assessments**

All subjects had two transthoracic echocardiograms, within 48 hours and after a median follow-up of 7 months (6 to 10 months). Echocardiograms were performed as described by Legallois *et al.* and obtained by experienced ultrasonographers who were blinded to the patients' plasma CoQ10 concentrations.<sup>21</sup> Adverse LVR was defined as a 20% increase in EDV between baseline and follow-up imaging sessions.<sup>24,25</sup>

**Statistical analysis**

Qualitative variables are shown as count and frequency (%). Quantitative variables are presented as mean $\pm$ SD or median and interquartile ranges when they had a skewed distribution. Continuous variables were compared using either the t-test or Wilcoxon rank sum test and categorical variables were compared by the  $\chi^2$  test or Fisher's exact test, depending on whether the data followed a normal distribution. Logistic regression models were carried out to assess the relationship between LVR and baseline parameters. All statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were 2-sided and used a significance threshold of  $p < 0.05$ .

## RESULTS

A total of 68 patients fulfilling complete biological data and echocardiography was included in the analysis. Demographic and clinical characteristics are summarized in Table 1. Median age was  $58.6 \pm 12.7$  years and 57 (83.8%) were men. Using the definition of adverse LVR as a 20% increase in EDV between baseline and follow-up echocardiography, we could discriminate an adverse LVR group (n=19, 28%) and a no adverse LVR group (n=49). As shown in Table 1, baseline characteristics were comparable between the 2 groups. Moreover, logistic regression models did not find any relationship between baseline parameters and LVR (Table 2). At baseline, LV end-diastolic and end-systolic volumes, as well as the LV ejection fraction, were similar between the two groups (Table 3) without significant association between LVR and LV volumes (Table 4). At 6-month follow-up, as expected, both LV end-diastolic and end-systolic volumes were significantly higher in the adverse LVR group compared to the no adverse LVR group. Biological data of interest for the study are depicted in Table 4 and Table 5. No significant differences were found between the adverse and no adverse LVR groups in regard to hs-cTnI and NT-proBNP levels. No difference in the lipid profile was observed either.

While investigating plasma CoQ10 concentration, values ranged from 0.46 to 2.21  $\mu\text{mol/L}$  but with no statistical difference between groups with and without LVR (mean  $1.21 \pm 0.41 \mu\text{mol/L}$  in the non-remodeling group,  $1.20 \pm 0.34 \mu\text{mol/L}$  in the remodeling group,  $p=0.89$ ) (Table 5 and Figure 1A). No significant relationship was found using logistic regression model between CoQ10 levels and LVR (Table 4). We found a similar positive correlation between CoQ10 and total cholesterol concentrations ( $r=0.605$ ;  $p<0.001$ ), as well as between CoQ10 and LDL-cholesterol concentrations ( $r=0.586$ ;  $p<0.001$ ) (Figure 2). In contrast, HDL-cholesterol level was not significantly related to CoQ10 concentrations ( $r=0.125$ ;  $p=0.360$ , data not shown). Thus, CoQ10 levels were indexed to LDL and total cholesterol. No statistical difference between both groups was observed either (Figure 1B and 1C).

Finally, skeletal muscle and plasma CoQ10 status was investigated in an independent series of 12 patients undergoing a muscle biopsy in our laboratory. Plasma CoQ10 values ranged from 0.42 to 2.04  $\mu\text{mol/L}$  and muscle values ranged from 50.00 to 1431.43  $\text{pmol/mg}$  of protein. We found no correlation between skeletal muscle and plasma CoQ10 concentrations (data not shown).

**Table 1.** Demographic and clinical characteristics of the study population. Data are presented as mean ( $\pm$  standard deviation) , median (quartiles) or as number (percentage).

|                                          | Overall Population | Left Ventricular Remodeling |                 | p     |
|------------------------------------------|--------------------|-----------------------------|-----------------|-------|
|                                          | (n=68)             | No (n=49)                   | Yes (n=19)      | Value |
| Age (years)                              | 58.65 (12.73)      | 58.62 (12.95)               | 58.74 (12.48)   | 0.97  |
| Male gender                              | 57 (83.8)          | 40 (81.6)                   | 17 (89.5)       | 0.72  |
| GFR (mL/min/1.73m <sup>2</sup> )         | 92.87 (16.89)      | 94.28 (15.67)               | 89.50 (19.56)   | 0.32  |
| BMI (kg/m <sup>2</sup> )                 | 27.37 (4.69)       | 27.75 (5.04)                | 26.39 (3.60)    | 0.29  |
| Smoking habit                            | 44 (64.7)          | 33 (67.3)                   | 11 (57.9)       | 0.57  |
| Hypertension                             | 25 (36.8)          | 19 (38.8)                   | 6 (31.6)        | 0.58  |
| Family history of cardiovascular disease | 12 (17.6)          | 9 (18.4)                    | 3 (15.8)        | 1     |
| Diabetes mellitus                        | 13 (19.1)          | 10 (20.4)                   | 3 (15.8)        | 1     |
| Hypercholesterolemia                     | 32 (47.1)          | 22 (44.9)                   | 10 (52.6)       | 0.57  |
| Heart rate (beats/min)                   | 77 (18)            | 77 (18)                     | 76 (18)         | 0.77  |
| Systolic blood pressure (mmHg)           | 142 (25)           | 142 (28)                    | 145 (19)        | 0.48  |
| Diastolic blood pressure (mmHg)          | 85 (19)            | 86 (20)                     | 82 (15)         | 0.50  |
| Symptoms to balloon (hours)              | 4.7 [3.2 ; 8.85]   | 4.7 [2.9 ; 9.7]             | 5.0 [3.6 ; 8.1] | 0.59  |
| Site of acute myocardial infarction      |                    |                             |                 |       |
| Anterior                                 | 28 (41.2)          | 19 (38.8)                   | 9 (47.4)        | 0.52  |
| Inferior                                 | 36 (52.9)          | 26 (53.1)                   | 10 (52.6)       | 0.97  |
| Lateral                                  | 19 (27.9)          | 14 (28.6)                   | 5 (26.3)        | 0.85  |
| Basal                                    | 4 (5.9)            | 3 (6.1)                     | 1 (5.3)         | 1     |
| Right ventricle                          | 5 (7.4)            | 4 (8.2)                     | 1 (5.3)         | 1     |

GFR=Glomerular Filtration Rate. BMI=Body Mass Index.

GFR: 7 data missing ; BMI: 1 data missing

**Table 2. Association between Left Ventricular Remodeling and baseline demographic/clinical factors**

|                                          |             | n  | Left Ventricular Remodeling |       | Crude RR* | 95% CI        | p    |
|------------------------------------------|-------------|----|-----------------------------|-------|-----------|---------------|------|
|                                          |             |    | n                           | %     |           |               |      |
| Age (years)                              |             | 68 |                             |       | 1.01      | (0.75 ; 1.35) | 0.97 |
| Gender                                   | Male        | 57 | 17                          | 29.8% | 1.64      | (0.44 ; 6.11) | 0.46 |
|                                          | Female      | 11 | 2                           | 18.2% | 1         |               |      |
| GFR (mL/min/1.73m <sup>2</sup> )         |             | 61 |                             |       | 0.87      | (0.69 ; 1.11) | 0.27 |
| BMI (kg/m <sup>2</sup> )                 |             | 67 |                             |       | 0.95      | (0.87 ; 1.04) | 0.31 |
| Smoking habit                            | No          | 43 | 13                          | 30.2% | 1         |               |      |
|                                          | Yes         | 25 | 6                           | 24.0% | 0.80      | (0.37 ; 1.72) | 0.57 |
| Hypertension                             | No          | 25 | 8                           | 32.0% | 1         |               |      |
|                                          | Yes         | 43 | 11                          | 25.6% | 0.79      | (0.35 ; 1.82) | 0.59 |
| Family history of cardiovascular disease | No          | 56 | 16                          | 28.6% | 1         |               |      |
|                                          | Yes         | 12 | 3                           | 25.0% | 0.88      | (0.30 ; 2.54) | 0.81 |
| Diabetes mellitus                        | No          | 55 | 16                          | 29.1% | 1         |               |      |
|                                          | Yes         | 13 | 3                           | 23.1% | 0.79      | (0.27 ; 2.32) | 0.67 |
| Hypercholesterolemia                     | No          | 36 | 9                           | 25.0% | 1         |               |      |
|                                          | Yes         | 32 | 10                          | 31.3% | 1.25      | (0.58 ; 2.68) | 0.57 |
| Heart rate (beats/min)                   |             | 68 |                             |       | 0.97      | (0.77 ; 1.21) | 0.77 |
| Systolic blood pressure (mmHg)           |             | 68 |                             |       | 1.049     | (0.91 ; 1.21) | 0.51 |
| Diastolic blood pressure (mmHg)          |             | 68 |                             |       | 0.99      | (0.81 ; 1.20) | 0.88 |
| Symptoms to balloon (hours)              |             | 68 |                             |       | 1.00      | (0.94 ; 1.07) | 0.96 |
| Antiplatelet agent                       | Ticagrelor  | 49 | 15                          | 30.6% | 1.53      | (0.25 ; 9.29) | 0.75 |
|                                          | Prasugrel   | 14 | 3                           | 21.4% | 1.07      | (0.14 ; 8.07) |      |
|                                          | Clopidogrel | 5  | 1                           | 20.0% | 1         |               |      |

\* Age, GFR, Heart Rate, Systolic and Diastolic blood pressure: for a 10-unit increase  
 BMI, Symptoms to balloon: for a 1-unit increase

**Table 3.** Changes in left ventricular characteristics on 3D-echocardiography. Data are presented as mean  $\pm$  standard deviation.

|                              | Overall Population<br>(n=68) | Left Ventricular Remodeling<br>No (n=49)      Yes (n=19) |               | p Value* |
|------------------------------|------------------------------|----------------------------------------------------------|---------------|----------|
| At baseline                  |                              |                                                          |               |          |
| End diastolic volume (mL/m²) | 54.38 (13.29)                | 55.39 (12.65)                                            | 51.75 (14.85) | 0.31     |
| End systolic volume (mL/m²)  | 30.45 (10.02)                | 30.65 (10.44)                                            | 29.93 (9.11)  | 0.79     |
| Ejection fraction (%)        | 44.32 (9.09)                 | 45.12 (9.95)                                             | 42.26 (6.11)  | 0.25     |
| At follow-up                 |                              |                                                          |               |          |
| End diastolic volume (mL/m²) | 57.31 (15.89)                | 52.63 (11.85)                                            | 69.38 (18.77) | 0.0014   |
| End systolic volume (mL/m²)  | 28.58 (11.90)                | 25.27 (8.94)                                             | 37.10 (14.40) | 0.0028   |
| Ejection fraction (%)        | 51.12 (9.65)                 | 52.57 (9.34)                                             | 47.37 (9.66)  | 0.045    |

**Table 4. Association between Left Ventricular Remodeling and baseline echocardiographic/biological factors**

|                                           | n         | Crude RR*   | 95% CI               | p           |
|-------------------------------------------|-----------|-------------|----------------------|-------------|
| End diastolic volume (mL/m <sup>2</sup> ) | 68        | 0.85        | (0.62 ; 1.15)        | 0.28        |
| End systolic volume (mL/m <sup>2</sup> )  | 68        | 0.95        | (0.65 ; 1.40)        | 0.79        |
| Ejection fraction (%)                     | 68        | 0.83        | (0.60 ; 1.16)        | 0.28        |
| Cardiac output (L/min)                    | 47        | 0.91        | (0.62 ; 1.33)        | 0.63        |
| hs-cTnI (pg/mL)                           | 67        | 1.01        | (0.98 ; 1.04)        | 0.45        |
| NT-proBNP (pg/mL)                         | 68        | 1.14        | (0.94 ; 1.38)        | 0.17        |
| Total cholesterol (mmol/L)                | 63        | 1.24        | (0.83 ; 1.86)        | 0.30        |
| LDL cholesterol (mmol/L)                  | 58        | 1.27        | (0.74 ; 2.18)        | 0.38        |
| HDL cholesterol (mmol/L)                  | 56        | 3.73        | (0.65 ; 21.44)       | 0.14        |
| Triglycerides (mmol/L)                    | 63        | 0.85        | (0.53 ; 1.37)        | 0.51        |
| <b>CoQ10 (μmol/L)</b>                     | <b>68</b> | <b>0.99</b> | <b>(0.90 ; 1.09)</b> | <b>0.89</b> |
| CoQ10/T-CHL (μmol/mmol)                   | 63        | 0.76        | (0.41 ; 1.40)        | 0.38        |
| CoQ10/LDL-CHL (μmol/mmol)                 | 58        | 0.79        | (0.52 ; 1.20)        | 0.27        |

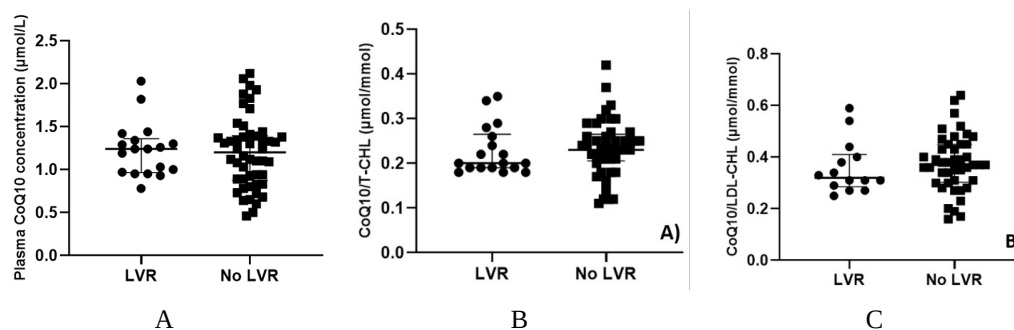
\* End diastolic and systolic volumes, Ejection fraction: for a 10-unit increase. Cardiac output, Total, LDL and HDL cholesterol, Triglycerides: for a 1-unit increase. hs-cTnI, NTproBNP: for a 1000-unit increase. CoQ10, CoQ10 / T-CHL, CoQ10 / LDL-CHL: for a 0.1-unit increase

**Table 5. Biological data at baseline according to LVR groups. Data are presented as mean ± standard deviation.**

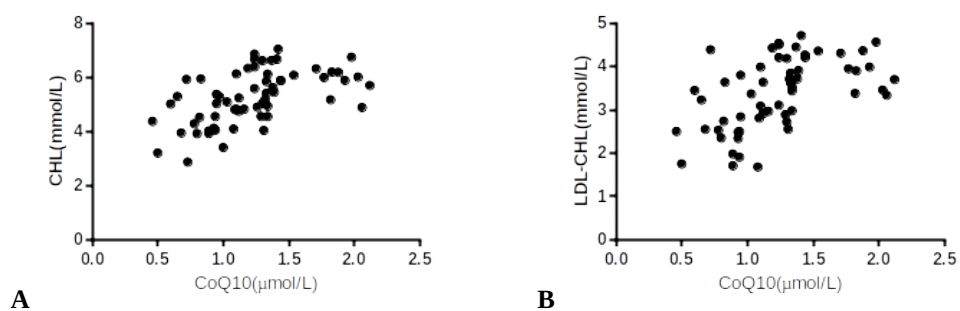
|                            | Overall Population | Left Ventricular Remodeling |                    | p     |
|----------------------------|--------------------|-----------------------------|--------------------|-------|
|                            | (n=68)             | No (n=49)                   | Yes (n=19)         | Value |
| hs-cTnI (pg/mL)            | 1947 (164 ; 9991)  | 2080 (164 ; 9906)           | 1556 (242 ; 10421) | 0.72  |
| NT-proBNP (pg/mL)          | 204 (66 ; 1040)    | 221 (74 ; 927)              | 177 (55 ; 1181)    | 0.68  |
| Total cholesterol (mmol/L) | 5.25 (0.98)        | 5.16 (0.98)                 | 5.44 (0.97)        | 0.30  |
| LDL cholesterol (mmol/L)   | 3.38 (0.82)        | 3.32 (0.87)                 | 3.55 (0.69)        | 0.37  |
| HDL cholesterol (mmol/L)   | 1.15 (0.26)        | 1.13 (0.22)                 | 1.23 (0.36)        | 0.22  |
| Triglycerides (mmol/L)     | 1.52 (1.02 ; 2.11) | 1.53 (1.06 ; 2.19)          | 1.36 (0.77 ; 1.80) | 0.40  |
| CoQ10 (μmol/L)             | 1.21 (0.39)        | 1.21 (0.41)                 | 1.20 (0.34)        | 0.89  |
| CoQ10/T-CHL (μmol/mmol)    | 0.23 (0.061)       | 0.24 (0.063)                | 0.22 (0.058)       | 0.39  |
| CoQ10/LDL-CHL (μmol/mmol)  | 0.37 (0.11)        | 0.38 (0.11)                 | 0.35 (0.11)        | 0.29  |

hs-cTnI: 1 data missing ; total cholesterol: 5 data missing ; LDL cholesterol: 10 data missing ; HDL cholesterol: 12 data missing ; triglycerides: 5 data missing.

**Figure 1.** Plasma CoQ10 concentration (A) and plasma CoQ10 concentration indexed to total cholesterol (T-CHL, B) or LDL cholesterol (LDL-CHL, C) according to adverse LVR and no adverse LVR groups. Bottom and top bands represent the 1<sup>st</sup> and 3<sup>rd</sup> quartile and middle band represent the median.



**Figure 2.** Correlation between plasma CoQ10 concentrations and total cholesterol (A) or LDL cholesterol (B).



## DISCUSSION

This study aimed to measure the plasma CoQ10 concentration in a cohort of patients who were admitted to hospital for STEMI in order to determine whether baseline CoQ10 level could be an early biomarker to predict adverse LVR at 6 months of follow-up. Among the 68 patients included in the study, 19 patients (28%) developed adverse LVR. This is in accordance with data from literature where postinfarct ventricular remodeling was found to develop in about 30% patients.<sup>26,27</sup> We found plasma CoQ10 concentrations ranging from 0.46 to 2.21  $\mu\text{mol/L}$  which are similar to those described in the literature.<sup>28</sup> For example, concentrations of total CoQ10 in plasma of healthy subjects have been reported (means  $\pm$  SD) with different methods: 0.675  $\pm$  0.315  $\mu\text{mol/L}$  (HPLC/MSMS),<sup>38</sup> 0.75  $\pm$  0.22  $\mu\text{mol/L}$  (HPLC with UV detection)<sup>29</sup> and 1.11  $\pm$  0.24  $\mu\text{mol/L}$  (HPLC with electrochemical detection).<sup>30</sup> As circulating CoQ10 is mainly transported by lipoproteins (about 58% with LDL and 26% with HDL), we studied their relationships and found a positive correlation between CoQ10 and total cholesterol concentrations ( $r=0.605$  ;  $p < 0.001$ ), as well as between CoQ10 and LDL-cholesterol concentrations ( $r=0.586$  ;  $p < 0.001$ ). This is also in accordance with results from Tomasetti *et al.* and Niklowitz *et al.* who found similar correlations with total cholesterol ( $r=0.63$ ,  $p < 0.001$ ) and LDL-cholesterol levels ( $r=0.57$ ,  $p < 0.001$ ).<sup>31,32</sup> However, we found no evidence that plasma CoQ10 concentrations at baseline were lowered in the remodeling group vs. non-remodeling patients.

The most probable hypothesis is that plasma CoQ10 concentrations may not accurately reflect tissue concentrations, particularly in cardiomyocytes where mitochondria account for about 25% of cell volume.<sup>33</sup> As with many biomarkers, CoQ10 status in humans is determined from plasma concentrations primarily because of easy sample collection. However, plasma and tissue CoQ10 contents exhibit several differences. In heart, CoQ10 is mainly intracellular and located within the mitochondrial inner membrane where it constitutes a 50/50 ubiquinone/ubiquinol pool that both participates in the respiratory chain and as antioxidant.<sup>34</sup> In plasma, CoQ10 is known to be carried by lipoproteins and is present almost entirely - about 95% - in its reduced form to protect lipoproteins from oxidative stress and lipid peroxidation.<sup>35</sup>

Furthermore, the correlation between tissue and plasma CoQ10 status is not obvious. For example, Duncan *et al.* found a close association between skeletal muscle and mononuclear cells CoQ10 concentration, but no correlation between skeletal muscle and plasma CoQ10 concentrations.<sup>36</sup> In this study we did not find any correlation between skeletal muscle and plasma CoQ10 concentrations either. A similar conclusion was drawn by Folkers *et al.* who showed no correlation between blood and heart CoQ10 concentrations. However, they observed low blood CoQ10 levels in patients suffering from cardiomyopathy but not as markedly as for the heart biopsies. Thus, they hypothesized that a correlation between plasma and organ levels may exist only

for the most severe deficiency state.<sup>37</sup> In our study, we found similar values of plasma CoQ10 concentrations to those described in the literature. So, based on the reference values obtained from controls in previous studies, we can rule out severe CoQ10 deficiency in our patients. Thus, this may explain the lack of correlation between plasma and cardiac CoQ10 concentrations and the absence of significant difference in CoQ10 levels between patients with and without adverse LVR.

The reason why the plasma and tissues CoQ10 levels are not correlated is probably due to the endogenous biosynthesis of this compound. In physiological conditions, tissue CoQ10 levels mainly depend on *de novo* synthesis. In contrast, plasma CoQ10 concentrations are significantly influenced by dietary uptake after incorporation within lipoproteins in the liver and release into the blood.<sup>38</sup> However, we could not ensure that the patients were on an empty stomach before PPCI and blood sample. Supplementation studies with labeled CoQ10 revealed that tissue uptake was limited mainly to the liver and plasma, indicating that heart CoQ10 content mainly relies on the endogenous synthesis.<sup>39</sup> This is also illustrated by the fact that exogenous CoQ10 does not down-regulate its endogenous synthesis.<sup>40</sup> The situation is however completely different when there is a severe deficiency in CoQ10 tissue level, for example in patients with a genetic deficiency of CoQ10 synthesis or in patients with heart failure who exhibit low levels of CoQ10 in cardiomyocytes. In those cases, the plasma uptake of exogenous CoQ10 is necessary to maintain adequate tissue levels, suggesting that tissue deficiency precedes plasma deficiency.

In a murine model of CoQ10 deficiency (ApoA1<sup>-/-</sup>), Dadabayev *et al.* observed significantly larger infarct size in ApoA1 null (ApoA1<sup>-/-</sup>) and ApoA1 heterozygous (ApoA1<sup>+/-</sup>) mice compared to wild-type (WT) mice.<sup>41</sup> They found a reduced cardiac CoQ10 pool in ApoA1<sup>-/-</sup> mice with impaired electron transfer from Complex II to Complex III. Administration of CoQ10 to ApoA1<sup>-/-</sup> mice normalized the myocardial CoQ10 level but had no effect in WT mice, showing that mitochondrial dysfunction directly arises from a pre-existing depleted pool of CoQ10 in cardiomyocytes. On the other hand, higher values than “normal” plasma CoQ10 concentrations seem to be necessary for an efficient uptake by peripheral tissues. For instance, in cardiovascular diseases, the achievement of a plasma threshold of at least 2.78 µmol/mL is necessary to observe a therapeutic benefit.<sup>37</sup> Thus, it would be interesting to investigate whether patients who exhibit a real plasma CoQ10 deficiency/overload would be more/less likely to develop LVR compared to patients with CoQ10 in the normal range.

Another point to consider is that we decided to investigate the plasma CoQ10 concentration at the onset of STEMI. In a similar study, Huang *et al.* examined the potential correlation between plasma CoQ10 level at baseline and 3 days, 7 days, and 1 month after STEMI and the LV performance. They found that CoQ10 levels gradually decreased with time and that lower CoQ10 concentrations in plasma at 1 month was predictive of adverse LVR 6 months after STEMI (adverse

LVR was defined as a 10% increase in ESV between baseline and follow-up).<sup>17</sup> However, they did not interpret the prognostic value of CoQ10 at the other measured times, suggesting that earlier measurements – particularly at baseline – were not predictive of LV performance as found in our study. It is thus likely that we did not find any evidence that circulating levels of CoQ10 were lowered before cardiac remodeling because the CoQ10 decrease might happen as a result from compensatory mechanisms that gradually fall into place after the onset of STEMI. This is consistent with all findings in patients with chronic heart failure where myocardial remodeling is already present and who exhibit low circulating and tissue levels of CoQ10.<sup>42</sup>

When we initially designed the study, we have not considered to take a blood sample at 6 months of follow-up and it would have been interesting to determine the CoQ10 concentration at that time. Another limitation is that we determined the amount of CoQ10 in its oxidized form but not the Ubiquinol (CoQ10H<sub>2</sub>)/Ubiquinone (CoQ10) ratio. However, measurement of both reduced and oxidized forms implies great technical considerations regarding sample processing and analytical stability.<sup>38</sup> Ubiquinol is readily oxidized to Ubiquinone during sample preparation or long-term storage, even at -80°C, which is the case in our study where the first samples were collected on January 2017 and analyzed two years later. A prospective study with immediate determination of CoQ10 redox state would be interesting as altered plasma ratios reflect oxidative stress and could be involved in the LV remodeling.<sup>38</sup>

In conclusion, we found no evidence for a role of circulating CoQ10 as an early biomarker for prediction of unfavorable LVR in patients with STEMI. As shown by a comparison between plasma and skeletal muscle, the plasma CoQ10 levels presumably do not accurately reflect CoQ10 content in cardiomyocytes.

#### **Authors' contributions**

FF performed the CoQ10 assays, analyzed the data and drafted the manuscript. DL extracted and analyzed the data and revised the manuscript. CC performed the statistical analysis. MC et LC participated to the CoQ10 assays. AH and ES carried out echocardiography imaging. PM revised the manuscript. FB and SA designed the study and revised the manuscript. All authors read and approved the final manuscript.

## REFERENCES

1. Puymirat E., Simon T., Cayla G., Cottin Y., Elbaz M., Coste P., Lemesle G., Motreff P., Popovic B., Khalife K., Labèque J.N., Perret T., Le Ray C., Orion L., Jouve B., Blanchard D., Peycher P., Silvain J., Steg P.G., Goldstein P., Guéret P., Belle L., Aissaoui N., Ferrières J., Schiele F., Danchin N. Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. *Circulation* **2017**, *136*, 1908-1919.
2. Cohn J.N., Ferrari R., Sharpe N. Cardiac remodeling – concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. *J. Am. Coll. Cardiol.* **2000**, *35*, 569-582.
3. Bauters C., Dubois E., Porouchani S., Saloux E., Fertin M., de Groote P., Lamblin N., Pinet F. Long-term prognostic impact of left ventricular remodeling after a first myocardial infarction in modern clinical practice. *PLoS One* **2017**, *12*, doi: 10.1371/journal.pone.0188884.
4. Xie M., Burchfield J.S., Hill J.A. Pathological ventricular remodeling: mechanisms: part 1 of 2. *Circulation* **2013**, *128*, 388-400.
5. Chow S.L., Maisel A.S., Anand I., Bozkurt B., de Boer R.A., Felker G.M., Fonarow G.C., Greenberg B., Januzzi J.L. Jr., Kiernan M.S., Liu P.P., Wang T.J., Yancy C.W., Zile M.R. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. *Circulation* **2017**, *135*, 1054-1091.
6. Fertin M., Dubois E., Belliard A., Amouyel P., Pinet F., Bauters C. Usefulness of circulating biomarkers for the prediction of left ventricular remodeling after myocardial infarction. *Am. J. Cardiol.* **2012**, *110*, 277-283.
7. Schirone L., Forte M., Palmerio S., Yee D., Nocella C., Angelini F., Pagano F., Schiavon S., Bordin A., Carrizzo A., Vecchione C., Valenti V., Chimenti I., De Falco E., Sciarretta S., Frati G. A review of the molecular mechanisms underlying the development and progression of cardiac remodeling. *Oxid. Med. Cell Longev.* **2017**, *2017*:3920195.
8. Holley C., Long E.K., Lindsey M.E., McFalls E.O., Kelly R.F. Recovery of hibernating myocardium: what is the role of surgical revascularization? *J. Card. Surg.* **2015**, *30*, 224-231.
9. Rababa'h A.M., Guillory A.N., Mustafa R., Hijawi T. Oxidative stress and cardiac remodeling: an updated edge. *Curr. Cardiol. Rev.* **2018**, *14*, 53-59.

10. Kaurola P., Sharma V., Vonk A., Vattulainen I., Rog T. Distribution and dynamics of quinones in the lipid bilayer mimicking the inner membrane of mitochondria. *Biochim. Biophys. Acta* **2016**, 1858, 2116-2122.
11. Lenaz G., Fato R., Formiggini G., Genova M.L. The role of Coenzyme Q in mitochondrial electron transport. *Mitochondrion* **2007**, 7S, S8-S33.
12. Bentinger M., Brismar K., Dallner G. The antioxidant role of coenzyme Q. *Mitochondrion* **2007**, 7S, S41-S50.
13. Turunen M., Olsson J., Dallner G. Metabolism and function of coenzyme Q. *Biochim. Biophys. Acta* **2004**, 1660, 171-199.
14. Eleawa S.M., Alkhateeb M., Ghosh S., Al-Hashem F., Shatoor A.S., Alhejaily A., Khalil M.A. Coenzyme Q10 protects against acute consequences of experimental myocardial infarction in rats. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2015**, 7, 1-13.
15. Ivanov A., Gorodetskaya E., Kalenikova E., Medvedev O. Single intravenous injection of CoQ10 reduces infarct size in a rat model of ischemia and reperfusion injury. *World J. Card. Dis.* **2013**, 3, 1-7.
16. Liang S., Ping Z., Ge J. Coenzyme Q10 regulates antioxidative stress and autophagy in acute myocardial ischemia-reperfusion injury. *Oxid. Med. Cell. Longev.* **2017**, 4, 1-12.
17. Singh R.B., Fedacko J., Mojto V., Pella D. Coenzyme Q10 modulates remodeling possibly by decreasing angiotensin-converting enzyme in patients with acute coronary syndrome. *Antioxidants* **2018**, 7, 99-109.
18. Huang C.H., Kuo C.L., Huang C.S., Tseng W.M., Lian B., Chang C.C., Liu C.S. High plasma coenzyme Q10 concentration is correlated with good left ventricular performance after primary angioplasty in patients with acute myocardial infarction. *Medicine* **2016**, 95, 31-37.
19. Pepe S., Marasco S.F., Haas S.J., Sheeran F.L., Krum H., Rosenfeldt F.L. Coenzyme Q10 in cardiovascular disease. *Mitochondrion* **2007**, 7S, S154-S167.
20. Sharma A., Fonarow G.C., Butler J., Ezekowitz J.A., Felker M. Coenzyme Q10 and heart failure: a state-of-the-art review. *Circ. Heart Fail.* **2016**, 9, e002639.
21. Legallois D., Macquaire C., Hodzic A., Allouche S., El Khouakhi I., Manrique A., Milliez P., Saloux E., Beygui F. Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction. *BMC Cardiovascular Disorders* **2020**, 20(1):316.
22. Ruiz-Jiménez J., Priego-Capote F., Mata-Granados J.M., Quesada J.M., Luque de Castro M.D. Determination of the ubiquinol-10 and ubiquinone-10 (coenzyme Q10) in human serum by liquid chromatography tandem mass spectrometry to evaluate the oxidative stress. *J. Chromatogr. A* **2007**, 1175, 242-248.

23. Smith P.K., Krohn R.I., Hermanson G.T., Mallia A.K., Gartner F.H., Provenzano M.D., Fujimoto E.K., Goeke N.M., Olson B.J., Klenk D.C. Measurement of protein using bicinchoninic acid. *Anal. Biochem.* **1985**, *150*, 76-85.
24. Urbano-Moral J.A., Lopez-Haldon J.E., Fernandez M., Mancha F., Sanchez A., Rodriguez-Puras M.J., Villa M., Lopez-Pardo F., Diaz de la Llera L., Valle J.I., Martinez A. Prognostic value of different serum biomarkers for left ventricular remodelling after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart* **2012**, *98*, 1153-1159.
25. Na H.M., Cho G.Y., Lee J.M., Cha M.J., Yoon Y.E., Lee S.P., Kim H.K., Kim Y.J., Sohn D.W. Echocardiographic predictors for left ventricular remodeling after acute ST elevation myocardial infarction with low risk group: Speckle tracking analysis. *J. Cardiovasc. Ultrasound* **2016**, *24*, 128-134.
26. Galli A., Lombardi F. Postinfarct left ventricular remodeling: A prevailing cause of heart failure. *Cardiol. Res. Pract.* **2016**, *18*, 2579832.
27. Huttin O., Coiro S., Selton-Suty C., Juilli re Y., Donal E., Magne J., Sadoul N., Zannad F., Rossignol P., Girerd N. Prediction of left ventricular remodeling after a myocardial infarction: role of myocardial deformation: a systematic review and meta-analysis. *PLoS ONE* **2016**, *11(12)*: e0168349.
28. Barshop B.A., Gangoiti J.A. Analysis of coenzyme Q in human blood and tissues. *Mitochondrion* **2007**, *7S*, S89-S93.
29. Sohmiya M., Tanaka M., Tak N.W., Yanagisawa M., Tanino Y., Suzuki Y., Okamoto K., Yamamoto Y. Redox status of plasma coenzyme Q10 indicates elevated systemix oxidative stress in Parkinson's disease. *J. Neurol. Sci.* **2004**, *223*, 161-166.
30. Niklowitz P., Menke T., Wiesel T., Mayatepek E., Zschocke J., Okun J.G., Andler W. Coenzyme Q10 in plasma and erythrocytes: comparison of antioxidant levels in healthy probands after oral supplementation and in patients suffering from sickle cell anemia. *Clin. Chim. Acta* **2004**, *326*, 155-161.
31. Niklowitz P., Onur S., Fischer A., Laudes M., Palussen M., Menke T., D ring F. Coenzyme Q10 serum concentration and redox status in European adults: influence of age, sex and lipoprotein concentration. *J. Clin. Biochem. Nutr.* **2016**, *58*, 240-245.
32. Tomasetti M., Alleva R., Solenghi M.D., Littarru G.P. Distribution of antioxidants among blood components and lipoproteins: significance of lipids/CoQ10 ratio as a possible marker of increased risk for atherosclerosis. *Biofactors* **1999**, *9*, 231-240.

33. Barth E., Stämmler G., Speiser B., Schaper J. Ultrastructural quantitation of mitochondria and myofilaments in cardiac muscle from 10 different animal species including man. *J. Mol. Cell. Cardiol.* **1992**, 24, 669-681.
34. Åberg F., Appelkvist E.L., Dallner G., Ernster L. Distribution and redox state of ubiquinones in rat and human tissues. *Arch. Biochem. Biophys.* **1992**, 295, 230-234.
35. Alleva R., Tomasetti M., Battino M., Curatola G., Littarru G.P., Folkers K. The roles of coenzyme Q10 and vitamin E on the peroxidation of human low density lipoprotein subfractions. *Proc. Natl. Acad. Sci. USA* **1995**, 92, 9388-9391.
36. Duncan A.J., Heales S.J., Mills K., Eaton S., Land J.M., Hargreaves I.P. Determination of coenzyme Q10 status in blood mononuclear cells, skeletal muscle, and plasma by HPLC with di-propoxy-coenzyme Q10 as an internal standard. *Clin. Chem.* **2005**, 51, 2380-2382.
37. Folkers K., Vadhanavikit S., Mortensen S.A. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. *Proc. Natl. Acad. Sci. USA* **1985**, 82, 901-904.
38. Bhagavan H.N., Chopra R.K. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Rad. Res.* **2006**, 40, 445-453.
39. Bentinger M., Dallner G., Chojnacki T., Swiezewska E. Distribution and breakdown of labeled coenzyme Q(10) in rat. *Free Radic. Biol. Med.* **2003**, 34, 563-575.
40. Bhagavan H.N., Chopra R.K. Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. *Mitochondrion* **2007**, 7S, S78-S88.
41. Dadabayev A.R., Yin G., Latchoumycandane C., McIntyre T.M., Lesnefsky E.J., Penn M.S. Apolipoprotein A1 regulates Coenzyme Q10 absorption, mitochondrial function and infarct size in a mouse model of myocardial infarction. *J. Nutr.* **2014**, 144, 1030-1036.
42. Garrido-Maraver J., Cordero M.D., Oropesa-Ávila M., Fernández Vega A., de la Mata M., Delgado Pavón A., de Miguel M., Pérez Calero C., Villanueva Paz M., Cotán D., Sánchez-Alcázar J.A. Coenzyme Q10 therapy. *Mol. Syndromol.* **2014**, 5, 187-197.

# Discussion

L'objectif de ce travail de thèse était donc d'apporter de nouveaux éléments dans la compréhension des mécanismes physiopathologiques conduisant à la survenue d'un RVG chez les patients ayant présenté un STEMI. Le RVG est un phénomène complexe, multifactoriel, faisant intervenir des mécanismes tels que l'inflammation, l'activation neuro-hormonale ou encore la bioénergétique cellulaire et en particulier du cardiomyocyte. Il est également communément admis que l'ensemble du myocarde – aussi bien la zone infarctée que la zone controlatérale, non directement concernée par l'occlusion coronaire – subit des modifications cellulaires et histologiques qui vont conduire au RVG.

## **Remodelage ventriculaire gauche post-infarctus: état des lieux des connaissances**

De très nombreux travaux, aussi bien précliniques que cliniques, ont cherché à expliquer la physiopathologie de survenue du RVG et à en chercher des facteurs prédictifs. La première partie de ce travail de thèse a donc consisté à un examen de l'état des lieux des connaissances sur ce sujet. Nous avons donc commencé par réaliser deux revues de la littérature, la première portant sur les critères de définition du RVG en IRM (page 12, [118]) et la seconde sur l'association entre les biomarqueurs dosés à la phase aiguë de l'infarctus et la survenue d'un RVG au cours du suivi (page 71).

Lors de la mise en place du registre RESIST, nous avons décidé d'étudier le RVG en ayant recours à l'échocardiographie. Ce choix a été porté par des raisons pratiques, la réalisation d'une échocardiographie à la phase aiguë d'un STEMI et au décours étant une pratique recommandée [1] et qui correspondait à nos habitudes sur le centre. Nous avons alors commencé ce travail de revue en incluant tous les articles qui avaient étudié le RVG après STEMI et ceci, quelle que soit la modalité d'imagerie utilisée. Nous avons ainsi retrouvé un total de 282 études et avons décidé de nous limiter alors aux 77 études utilisant l'IRM comme modalités d'imagerie, considérant sa meilleure reproductibilité pour la mesure des volumes VG [54] et la possibilité d'analyser des critères tels que la fibrose ou encore la taille de l'infarctus. La revue de la littérature portant sur la définition du RVG dans les études cliniques utilisant l'IRM a permis de montrer que la prévalence du RVG varie entre 11,3% et 48,4% dans les études ayant utilisé une valeur de seuil d'augmentation des volumes ventriculaires au cours du suivi (prévalence groupée de 22,8% ; IC<sub>95%</sub>[19,4% – 26,7%]) [118]. Ce travail a aussi permis de mettre en évidence la grande hétérogénéité de la littérature sur le sujet. En effet, il n'existe aucun consensus dans la quantification du RVG après un infarctus. Malgré une littérature très abondante sur le sujet, il n'existe pas d'études ayant une méthodologie reproductible concernant les points suivants : modalité d'imagerie utilisée, définition du remodelage (simple valeur du volume ventriculaire gauche et donc variable quantitative ou alors valeur seuil de remodelage permettant de séparer les patients présentant un RVG de ceux qui ne remodelent pas), mais aussi délai entre la survenue de l'infarctus et la première imagerie et délai entre l'examen initial et l'examen de suivi. L'examen des études d'IRM montre par ailleurs que la mesure des volumes ventriculaires n'est pas la seule à donner lieu à une hétérogénéité de sa quantification. Nous avons initialement envisagé stratifier les résultats obtenus dans les études en fonction de la taille de l'infarctus en IRM mais la méthodologie diffère aussi d'une étude à l'autre notamment sur le délai de réalisation de la première IRM [119, 120]. Or, il est probablement préférable que l'imagerie initiale

n'ait pas lieu durant la première semaine post-infarctus, avant la fin de la période de stunning et le début de la régression des processus inflammatoires et œdémateux [119].

Les patients inclus dans les études de remodelage sont également particulièrement sélectionnés et ne représentent pas un échantillon représentatif des patients se présentant en salle de cathétérisme pour une angioplastie primaire. Dans notre revue de la littérature portant sur la définition en IRM du RVG, l'âge médian ou moyen des patients inclus dans les études est de 59 ans, avec une FEVG moyenne ou médiane de 48,6% et un taux plus élevé de recours à l'angioplastie primaire que des registres publiés *a posteriori* de certaines de ces études [121]. Plus du quart des patients inclus dans notre travail étaient initialement inclus dans des études randomisées. Ces patients étaient donc sélectionnés et l'objectif initial de l'étude à laquelle ils étaient initialement inclus n'avait pas toujours un lien avec l'étude du RVG, l'analyse post-hoc étant faite rétrospectivement sur des données prospectivement acquises. Notre seconde revue portant sur le lien entre biomarqueurs et RVG permet elle aussi d'affirmer que les patients inclus dans les études de remodelage sont très sélectionnés. Nous avons retrouvé 25 études qui renseignent les valeurs de créatininémie ou d'estimation du débit de filtration glomérulaire dans leur population. La créatininémie moyenne de ces patients varie entre 68 et 96  $\mu\text{mol/L}$  (après éventuelle conversion de l'unité de mesure). Le débit de filtration glomérulaire estimé est entre 71 et 113  $\text{mL/min/1,73m}^2$ . Ces chiffres sont manifestement éloignés des patients pris en charge en angioplastie primaire, montrant bien la grande sélection des patients inclus dans ces études.

D'autres éléments objectifs d'ordre méthodologique doivent être soulignés comme limites à ces nombreuses études. Le premier est bien évidemment la taille des effectifs, certains travaux incluant parfois à peine une quarantaine de patients. Nous avons par ailleurs étudié la qualité des études observationnelles incluses dans notre travail, aussi bien concernant les

études observationnelles (pages 168 et 179, en annexe) que les études post-hoc d'essais randomisés (page 180). Une grande partie de ces travaux présentent des risques de biais, que ce soit sur la sélection des patients, le manque d'information concernant le suivi (notamment les événements cardiovasculaires majeurs) ou sur la méthodologie des mesures effectuées (par exemple l'absence de core lab d'échocardiographie). Enfin, certaines cohortes de patients ont été publiées à plusieurs reprises, utilisant des critères de définition du RVG qui pouvaient varier d'une étude à l'autre.

Cette problématique de reproductibilité des résultats a été retrouvée dans notre second travail de revue portant sur le lien entre biomarqueurs et RVG. En dehors des problématiques de définition du RVG que nous avons déjà évoqué, nous avons mis en évidence que la capacité d'un biomarqueur à prédire la survenue du RVG était grandement variable d'une étude à l'autre, surtout lorsqu'il s'agit de dosages qui ne sont pas réalisés en pratique clinique courante (page 73). Cette absence de reproductibilité liée à l'absence de standardisation des dosages est multifactorielle. Elle repose tout d'abord sur des limites intrinsèques aux kits utilisés: (i) les anticorps utilisés sont différents d'une trousse à l'autre, (ii) il n'existe pas de contrôle qualité comme pour les dosages en routine, (iii) il existe également une grande variabilité interexpérience et (iv) une absence de valeurs usuelles qui peuvent compliquer l'interprétation des résultats. L'autre point fondamental est la chronologie du prélèvement, qui doit être en adéquation avec la place du biomarqueur dans la physiopathologie du processus de remodelage. A titre d'exemple, nous avons ainsi identifié dans notre revue plusieurs études où les peptides natriurétiques ont été dosés plusieurs fois au cours du suivi [122–124, 102, 125]. Dans toutes ces études le dosage précoce des peptides natriurétiques – avant que l'activation neuro-hormonale n'ait pu vraiment débiter – n'est pas prédictif de la

survenue du RVG au cours du suivi alors que le dosage réalisé à la sortie d'hospitalisation du patient y est significativement associé, dans les mêmes publications.

Il est fondamental d'aborder la problématique de la valeur pronostique du RVG. En effet, tout le travail réalisé jusqu'alors de définition du RVG puis de recherche de facteurs prédictifs de survenue n'a de sens que si le fait de mettre en évidence un remodelage délétère chez un patient donné nous apporte une information sur son pronostic, dans le but ensuite d'impacter sur sa prise en charge. Ces données sont absentes de la plupart des études que nous avons incluses dans nos travaux de revue. Les études qui ont initialement décrit le RVG comme un facteur de mauvais pronostic après STEMI ont maintenant 20 ans [54, 126]. Depuis, la prise en charge de ces patients a radicalement évolué avec une réduction des délais de prise en charge, une meilleure anti-agrégation plaquettaire à la phase aiguë, un développement des techniques de revascularisation myocardique et une meilleure prise en charge au décours de l'infarctus [127]. Plusieurs études publiées très récemment, postérieurement au début de ce travail de thèse, remettent en question le caractère pronostique du RVG après un STEMI. Ainsi, une équipe autrichienne a récemment proposé de rechercher quel paramètre de remodelage est associé à la survenue d'évènements cardio-vasculaires majeurs au décours d'un STEMI [128]. L'augmentation du volume télédiastolique d'au moins 10% à 4 mois est associé à un risque relatif de 8,68 ; IC<sub>95%</sub>[2,39 – 31,56] dans cette cohorte de 224 patients où seulement 13 (6%) ont eu un évènement cardio-vasculaire majeur à 24 mois. Deux études publiées en 2019 vont à l'encontre d'un intérêt de l'évaluation du RVG dans un but pronostique. L'étude de Rodriguez-Palomares a inclus 374 patients ayant eu une IRM à la phase initiale et 6 mois après un STEMI et ne retrouve pas d'apport pronostique d'un critère de remodelage défini par une augmentation de plus de 15% du volume télédiastolique associé à une diminution de plus de 3% de la FEVG sur la prédiction des évènements cardio-vasculaires majeurs par rapport aux données de l'IRM initiale seulement [129]. L'équipe de Masci a inclus

492 patients ayant eu une IRM à la phase initiale et 4,8 mois après le STEMI. Le critère de jugement principal composite – comprenant décès toutes causes et hospitalisation pour IC – est survenu chez 84 patients après un délai moyen de 8,3 ans [130]. Aucun des deux critères les plus communément retrouvés pour définir un RVG (augmentation du volume télédiastolique  $>20\%$  et augmentation du volume télésystolique  $>15\%$ ) n'a permis de prédire indépendamment la survenue d'un évènement. Ces études ont tout de même des limites. La population est ici aussi sélectionnée, et est l'agrégat de plusieurs cohortes plus petites dont certaines ont été incluses il y a plus de 15 ans comme en témoigne les caractéristiques des patients à l'inclusion (par exemple, seulement  $\frac{2}{3}$  des patients ont bénéficié d'une angioplastie primaire dans les 12 heures suivant le début de la symptomatologie [129]). L'utilisation d'une variation de 3% de la FEVG dans la définition du remodelage pose problème vis-à-vis de la reproductibilité de la mesure [131]. Une dernière étude, elle aussi publiée en 2019 a inclus 1995 patients depuis 2004 [132]. Les patients ont été classés en quatre groupes : remodelage précoce en cas d'augmentation d'au moins 20% du volume télédiastolique dans les 3 mois suivant le STEMI (613 patients, 30,7%), remodelage à moyen terme si cette augmentation de volume survient entre le 3<sup>e</sup> et le 6<sup>e</sup> mois (216 patients, 10,8%), remodelage tardif si l'augmentation de volume est observée entre le 6<sup>e</sup> et le 12<sup>e</sup> mois (124 patients, 6,2%). Enfin, les patients n'ayant jamais eu une augmentation de volume télédiastolique du VG de plus de 20% sont classés dans un groupe sans remodelage (1042 patients, 52,2%). Il n'existe pas de différence en terme de mortalité au terme d'un suivi médian de 94 mois. En revanche, les patients ayant un RVG au cours du suivi sont plus fréquemment hospitalisés pour IC (risque relatif: 2,81 ; IC<sub>95%</sub>[1,78 – 4,42],  $p<0,001$  en analyse univariée et 2,66 ; IC<sub>95%</sub>[1,69 – 4,19],  $p<0,001$  en analyse multivariée). Ce sur-risque est retrouvé dans les sous-groupes FEVG $<40\%$  et FEVG entre 40 et 49% mais pas dans le groupe FEVG $\geq 50\%$  et après analyse de sensibilité basée sur la valeur initiale du volume télédiastolique VG.

L'ensemble de ces travaux et de ces résultats nous conduisent donc à plaider pour une homogénéisation des pratiques concernant les études portant sur le RVG. La position de Bulluck et al. consistant à prendre en compte l'évolution des volumes ventriculaires télé-diastolique et télésystolique [133] est intéressante car elle permet de séparer les patients selon différents modèles de remodelage ventriculaire. En effet, le volume télédiastolique est plutôt en rapport avec le remodelage "macroscopique" du VG et la précharge alors que le volume télésystolique est plutôt dépendant des conditions de charge et de la capacité des fibres à se contracter [51]. Ces deux aspects sont importants, et, à augmentation de volume télédiastolique équivalente, il existe des arguments pour penser que le profil évolutif n'est pas le même chez un patient ayant augmenté significativement son volume télésystolique et altéré sa FEVG par rapport à un patient ayant compensé son remodelage ventriculaire par une augmentation de son volume télésystolique avec pour conséquence, un maintien de sa FEVG [132]. Cette approche devra à l'avenir être validée dans des cohortes de grandes tailles afin de pouvoir aussi évaluer l'impact pronostique de la survenue d'un RVG, chez des patients non sélectionnés et ayant bénéficié à la phase aiguë des stratégies modernes de reperfusion myocardique. Il est probablement préférable que l'évaluation du RVG se fasse précocement, environ 3 mois après la survenue du STEMI. En effet, les études d'imagerie sériées montrent que l'essentiel de l'évolution des volumes VG est observable dès le 3<sup>ème</sup> mois [134, 135] chez les patients qui évoluent vers un RVG. Le dépistage précoce de ces patients pourrait à terme peut être faire envisager une optimisation de leur traitement, en utilisant les classes thérapeutiques recommandées dans l'IC post-infarctus, et notamment les bloqueurs du SRAA [1, 30]. Ainsi, il a été montré que les patients qui ont un RVG et une FEVG inférieure à 50% au cours du suivi sont plus souvent ré-hospitalisés pour IC [132], ce qui pourrait être alors l'occasion de modifier leur traitement au profit d'un ARNI en remplacement de leur inhibiteur de l'enzyme de conversion de l'angiotensine (IEC) ou de leur antagoniste du récepteur AT<sub>1</sub> de l'angiotensine-II (ARA2) [107]. Dans une étude

préclinique, le traitement par ARNI a montré une supériorité par rapport au valsartan pour prévenir la dégradation de la FEVG [136]. Quant à la création de modèles prédictifs de survenue du RVG, la complexité de sa physiopathologie impose probablement une approche multiparamétrique associant données cliniques, d'imagerie et biologiques.

### **Nouveaux paramètres échocardiographiques et remodelage ventriculaire gauche en post-infarctus**

De nombreux paramètres d'imagerie sont décrits comme étant prédictifs de la survenue d'un RVG au cours du suivi, comme par exemple l'obstruction micro-vasculaire en IRM [61, 62], la taille de la zone infarctée [58–60] ou encore le strain longitudinal global du VG en échocardiographie [55, 56]. Ces paramètres ont en commun une évaluation – directe ou indirecte – de l'impact de l'infarctus sur la fonction systolique du VG. Le processus de remodelage post-infarctus n'étant pas exclusivement lié à l'atteinte de la fonction contractile de la zone infarctée, nous avons donc souhaité étudier l'implication d'autres paramètres: la zone *remote* non directement concernée par l'occlusion coronaire, la fonction atriale gauche et la fonction diastolique du VG par l'étude du GPIVD.

L'étude REMOD-TEP avait pour but de quantifier la fonction endothéliale coronaire et la fibrose dans le territoire de l'infarctus mais également dans le territoire non directement atteint par l'occlusion coronaire, chez 30 patients admis pour STEMI et ayant une atteinte mono-tronculaire à la coronarographie, en utilisant une imagerie TEP, un radiopharmaceutique librement diffusible (l'eau marquée à l'oxygène-15) et un test au froid (cf. page 28). L'étude n'ayant pu actuellement être menée à son terme pour des raisons matérielles, nous ne discuterons pas davantage ce point ici. Simplement, depuis l'écriture de

ce protocole en 2015, il existe désormais des données dans la littérature sur le rôle de la zone *remote* dans la survenue du RVG post-infarctus, chez l'homme [64–66].

Dans le travail portant sur la fonction OG dans une sous-population de 121 patients de notre registre RESIST, nous avons analysé le lien entre la survenue du RVG et les 3 composantes du strain atrial, évaluées 24 à 48 heures après la survenue de l'infarctus: (i) la fonction réservoir, dépendante de la relaxation et de la compliance atriale et de la descente du plancher basal du ventricule gauche durant la systole ventriculaire [137, 138], (ii) la fonction conduit, dépendante de la fonction diastolique du ventricule gauche et notamment de la succion du ventricule gauche, lorsque la valve mitrale est ouverte en début de diastole [139], et (iii) la fonction contractile, fonction de la contractilité atriale gauche, de la compliance du VG et des PRVG [140].

Il a été montré que la fonction réservoir de l'OG permet de limiter l'augmentation de la pression atriale secondaire à l'altération de la FEVG, et ainsi de maintenir des PRVG adaptées [141]. Dans notre étude, nous n'avons pas retrouvé de corrélation entre la composante réservoir du strain de l'OG ou le volume de l'OG d'une part et le RVG d'autre part. Il est possible que cette absence de corrélation soit en rapport avec des PRVG plutôt basses dans notre population de patients sans signe clinique d'IC, comme en atteste les différents indicateurs de fonction diastolique (rapport  $\frac{E}{A} = 0,96$  [0,84 – 1,20] ; temps de décélération de l'onde E mitrale = 200 ms [170 – 235] et rapport  $\frac{E}{e'} = 8,1$  [7,1 – 9,9]). D'après les recommandations 2016 concernant l'évaluation de la fonction diastolique [72], deux tiers de nos patients ont une pression atriale normale et une dysfonction diastolique de grade 1, trois patients ont une élévation de la pression OG et une dysfonction diastolique de grade 2 et trois patients ont une élévation de la pression OG et une dysfonction diastolique de grade 3. En raison d'une discordance entre le ratio  $\frac{E}{e'}$  et le volume indexé de l'OG chez les patients ayant un

rapport  $\frac{E}{A}$  entre 0,8 et 2 ou  $\leq 0,8$  avec une onde  $E \geq 50$  cm/s, il n'est pas possible de statuer sur le niveau de pression OG et le grade de dysfonction diastolique dans 31% de notre population.

Dans notre étude, seule la composante contractile du strain OG est corrélée à la survenue d'un RVG au décours du STEMI. Les liens qui existent entre fonction pompe atriale gauche et fonction systolique VG sont étroits. L'altération de la fonction systolique VG est un facteur indépendant d'altération de la fonction pompe atriale [142], via une élévation des PRVG. Inversement, l'altération de la fonction pompe de l'oreillette va altérer le remplissage du VG, diminuer le volume télédiastolique VG et ainsi altérer la FEVG et le débit cardiaque. Il est possible d'expliquer l'association entre une altération de la composante contractile du strain atrial à la phase sub-aiguë de l'infarctus et la survenue d'un RVG au cours du suivi. En effet, l'altération de la fonction pompe peut être un marqueur indirect d'une diminution de la compliance VG secondaire à l'infarctus [143]. Cette anomalie de la compliance va induire une élévation des PRVG, puis une activation des mécanismes neuro-hormonaux, dont les effets délétères au long cours vont conduire au RVG [144]. Dans le cercle vicieux qui lie fonction contractile atriale, fonction systolique ventriculaire gauche puis RVG, il existe des arguments dans notre étude pour dire que c'est l'anomalie de la fonction contractile atriale qui est l'élément déclencheur. Premièrement, les valeurs de la composante contractile du strain atrial restent associées au RVG indépendamment des volumes ventriculaires initiaux. Ensuite, l'altération du strain contractile atrial précède l'existence du RVG. Enfin, il est probable que les PRVG soient basses dans notre cohorte de patients sans signe clinique d'IC, comme précisé précédemment.

Dans notre étude, nous n'avons pas retrouvé de corrélation entre les valeurs de la composante conduit du strain OG et l'existence d'un RVG au cours du suivi. Il est possible ici aussi que l'inclusion de patients sans signe clinique d'IC explique en partie ce résultat, en

sélectionnant des patients ayant une compliance VG relativement conservée et des PRVG non élevées. Il a été également montré que dans le contexte de SCA, la composante contractile atriale peut être transitoirement améliorée afin de partiellement compenser une altération de la composante conduit [145]. Dans notre seconde étude d'imagerie, la valeur du GPIVD, secondaire à la détorsion du VG, contribuant ainsi à un phénomène de succion en début de diastole [146], n'est pas prédictrice de la survenue du RVG dans cette même population de patients admis pour un STEMI sans signe clinique d'IC. En dehors du temps de décélération de l'onde E (groupe  $RVG\oplus$ : 200 ms [170 – 240] vs. groupe  $RVG\ominus$ : 180 ms [153 – 230] ;  $p=0.046$ ), les autres paramètres recommandés pour l'évaluation de la fonction diastolique ne sont pas prédictifs de RVG (rapport  $\frac{E}{A}$ , rapport  $\frac{E}{e'}$  et taille de l'OG indexée). La valeur prédictrice d'un RVG de ces mêmes paramètres de fonction diastolique est controversée, que ce soit concernant le volume OG indexé [76, 55], le rapport  $\frac{E}{A}$  [75, 55, 77], le temps de décélération de l'onde E [77, 76] ou encore le rapport  $\frac{E}{e'}$  [76, 75]. La dysfonction diastolique est un processus complexe, associant une anomalie de la relaxation (notamment de la succion en début de diastole) et une diminution de la compliance ventriculaire. En pratique quotidienne, la dysfonction diastolique ne peut être affirmée sur un paramètre, mais sur un faisceau d'arguments [72]. Dès lors, il est possible que la valeur prédictrice d'un paramètre de fonction diastolique pris isolément – comme le GPIVD – ne soit pas suffisante pour être discriminante.

Ces deux études ont par ailleurs des limites communes, notamment méthodologiques. Le nombre de patients inclus est modeste, principalement limité par le fait que les patients ne sont pas reconvoqués dans le centre à titre systématique mais uniquement s'ils habitent dans l'aire urbaine caennaise et par les problématiques liées au serveur ayant conduit à la perte d'examens. La population incluse est sélectionnée, avec notamment exclusion des patients non revascularisés en phase aiguë, ayant des signes cliniques d'IC ou présentant une mauvaise échogénicité sur la session d'imagerie initiale. Enfin, il existe une importante

variabilité entre les logiciels existants pour la quantification du strain de l'OG [73] et du GPIVD [82]. Ce dernier point est un frein à la reproductibilité des résultats puis, dans un second temps, à la diffusion de la technique de quantification.

### **Nouveaux paramètres biologiques et remodelage ventriculaire gauche en post-infarctus**

Lors de la phase initiale de ce travail, nous avons envisagé mesurer les taux sériques de matrix metalloproteinase (MMP)s, CRP ultra-sensible, fibrinogène, interleukines et cytokines chez les patients du registre RESIST pour lesquels nous allions disposer des données échocardiographiques et de prélèvements biologiques réalisés à la phase aiguë du SCA. Nous avons ensuite conduit notre revue de la littérature, mettant en évidence qu'il existe déjà des données en faveur d'une association entre les taux sériques des marqueurs de nécrose myocardique, des peptides natriurétiques, des protéines de l'inflammation et du remodelage matriciel, notamment les MMPs. Ce sont donc principalement et logiquement des biomarqueurs qui ont un rapport – direct ou indirect – avec l'étendue de la nécrose qui sont associés à un risque de survenue du RVG. Plus les lésions de nécrose sont importantes, plus il y a une activation de l'inflammation, une élévation des pressions de remplissage et une activation des systèmes neuro-hormonaux, mais aussi une plus grande dégradation de la matrice extracellulaire et plus de fibrose. Devant ces résultats, nous avons choisi d'explorer d'autres axes, nous conduisant ainsi à étudier successivement la néprilysine et le coenzyme Q10.

Nous nous sommes donc intéressés à la néprilysine, endopeptidase neutre qui hydrolyse et inactive divers peptides, dont les peptides natriurétiques, la bradykinine ou encore l'adrénomédulline [105, 106]. La néprilysine a ainsi une position centrale dans les systèmes neuro-hormonaux, et son inhibition – associé à un ARA2 – a montré une supériorité par

rapport au traitement par IEC sur la réduction de la mortalité et des hospitalisations pour IC chez des patients ayant une FEVG  $\leq 40\%$  [107]. L'utilisation d'un ARNI dans cette même population a permis d'obtenir une réduction des volumes ventriculaires à 4 mois [147]. Dans notre étude, nous avons dosé la néprilysine sur un prélèvement sanguin réalisé au moment de la procédure de revascularisation coronaire chez 68 patients du registre RESIST [148]. Le taux de néprilysine n'est pas associé à la survenue d'un RVG mais est corrélé au stunning, les patients ayant les plus hauts niveaux de néprilysine ont une FEVG plus basse lors de l'échocardiographie initiale et ont la meilleure augmentation de FEVG au terme du suivi. Par ailleurs, nous n'avons pas retrouvé de corrélation entre les niveaux sériques de néprilysine et de NT-proBNP, comme cela avait déjà été mis en évidence antérieurement dans une large cohorte [149]. Les taux de néprilysine que nous avons mesurés sont comparables à ceux obtenus dans une étude lyonnaise récente dans une population de 203 patients hospitalisés pour STEMI [150]. Dans cette dernière étude, il n'existe pas de variation significative du dosage de néprilysine au cours du premier mois. Aussi, les taux de néprilysine ne sont pas corrélés ni à la taille de l'infarctus, ni à la FEVG, évaluées une seule fois en IRM à 1 mois de l'épisode. D'autres données, acquises dans une large population sans pathologie cardiovasculaire connue a montré que les patients ayant les taux les plus bas de néprilysine sont plus fréquemment fumeurs, hypertendus ou ayant une dysfonction diastolique [149], des situations où la fonction endothéliale est fréquemment altérée. La méthodologie de notre étude ne nous permet pas de lier le taux de néprilysine et le stunning d'une part et la régulation des peptides agissant sur la fonction endothéliale par la néprilysine d'autre part. Il sera peut-être possible d'avancer davantage sur point avec les données de fonction endothéliale coronaire qui seront acquises dans le cadre de l'étude REMOD-TEP.

Dans notre autre étude, nous avons étudié la relation entre le taux de CoQ10 et la survenue d'un RVG au cours du suivi. Dans une étude préclinique, le prétraitement par CoQ10 a permis une diminution de la taille de l'infarctus et également de préserver la fonction ventriculaire en diminuant le stress oxydatif par diminution de la production de facteurs pro-inflammatoires et pro-apoptotiques [151]. Il existe quelques données chez l'homme également, la supplémentation en CoQ10 pourrait permettre de limiter le RVG chez des patients ayant une FEVG inférieure à 50% en post-infarctus [152]. Aussi, il a été montré que la concentration plasmatique en CoQ10 à 1 mois du STEMI est corrélée avec la survenue d'un remodelage [153]. Toutes ces données suggèrent une possible implication du CoQ10 dans la survenue du RVG après STEMI, en particulier via la préservation des fonctions mitochondriales et la diminution de la production d'ERO [154, 155]. En effet, une partie des lésions d'ischémie-reperfusion sont secondaires à un dysfonctionnement de la fonction mitochondriale conduisant notamment à une production d'ERO [113]. Dans notre étude, nous avons donc dosé le CoQ10 chez 68 patients de notre registre RESIST pour lesquels nous disposions de données échocardiographiques complètes, à la phase initiale et au cours du suivi, mais aussi de prélèvements sanguins prélevés sur tubes EDTA, au moment de la procédure de revascularisation coronaire. Nous avons retrouvé des valeurs de CoQ10 entre 0,46 et 2,21  $\mu\text{mol/L}$ , valeurs similaires à celles retrouvées dans la littérature [156]. De plus, le CoQ10 étant principalement transporté par des lipoprotéines, les corrélations que nous avons trouvées avec les taux de cholestérol total et LDL-cholestérol sont également similaires à celles décrites dans la littérature [157, 158]. En revanche, nous n'avons pas trouvé d'association entre les taux sériques de CoQ10 à la phase aiguë du STEMI et le RVG au cours du suivi. Plusieurs explications peuvent être avancées pour expliquer ces résultats. Tout d'abord, la concentration plasmatique de CoQ10 n'est pas un reflet de la concentration tissulaire, en particulier dans les cardiomyocytes dont la composition en mitochondrie est importante [159]. Par ailleurs, dans la circulation sanguine, le CoQ10 est lié à des lipopro-

téines sous sa forme réduite afin de les protéger de l'oxydation [160]. Nous avons observé des résultats comparables en ne retrouvant aucune corrélation entre les taux plasmatiques de CoQ10 et le taux retrouvé dans les biopsies musculaires de 12 patients explorés dans le cadre d'une suspicion de maladie mitochondriale. Il existe d'autres arguments indiquant que le taux plasmatique de CoQ10 n'est pas un bon marqueur de son activité au sein des mitochondries des cardiomyocytes. La supplémentation par CoQ10 marqué ne retrouve pas ou peu de fixation au niveau cardiaque, soulignant l'importance de sa synthèse endogène [161]. Nous avons abordé précédemment l'importance du délai entre le début du STEMI et la réalisation du prélèvement. Dans notre étude, nous n'avons pas mis en évidence de lien entre la concentration plasmatique de CoQ10 à la phase aiguë de l'infarctus et le RVG. Dans une étude similaire, le taux plasmatique de CoQ10 avait été évalué 3 jours, 7 jours et 1 mois après le STEMI [153]. Le taux de CoQ10 diminuait progressivement au cours du temps et les patients avec les taux les plus bas de CoQ10 à 1 mois de l'épisode évoluaient plus souvent vers un RVG.

Nos deux études ont donc cherché à évaluer si la néprilysine d'une part et le CoQ10 d'autre part peuvent être des marqueurs pronostiques de l'évolution vers un RVG au décours d'un STEMI. Ces deux études sont donc négatives sur ce point et présentent des limites similaires. Il s'agit dans les deux cas d'une petite cohorte incluant des patients sélectionnés, où le biomarqueur d'intérêt n'a été dosé qu'une seule fois, à la phase aiguë du STEMI. Il existe probablement un intérêt à conduire d'autres études sur le sujet, sur une population de plus grande taille et moins sélectionnée, et en prenant en compte les limitations des études de ce manuscrit afin d'axer les recherches sur les éventuels mécanismes impliquant l'activation neuro-hormonale et la bioénergétique cellulaire des cardiomyocytes dans la survenue d'un RVG post-infarctus.

## **Perspectives**

Ce travail de thèse ouvre des perspectives pour les recherches futures. Il existe un besoin d'une clarification de la notion de RVG en post-infarctus, notamment en ce qui concerne sa définition et la méthodologie à utiliser pour le mesurer. La standardisation des pratiques est un point important car elle permet d'augmenter la puissance des analyses à l'heure du développement des procédures de data mining. Il est important d'évaluer le caractère pronostique du RVG, dans une population de patients non sélectionnés. Les paramètres – cliniques, biologiques et d'imagerie – qui ont jusqu'ici été montrés comme étant prédictifs de la survenue d'un RVG doivent être validés prospectivement dans de telles cohortes. Ce pré-requis est indispensable à une approche multiparamétrique dans le but d'identifier puis de traiter le plus précocement possible les patients à plus haut risque de RVG durant le suivi.

## Conclusion

Nos travaux ont donc essayé de mieux comprendre les mécanismes impliqués dans la survenue du remodelage ventriculaire gauche au décours d'un syndrome coronarien aigu avec sus-décalage du segment ST en utilisant une approche multiple. Les résultats que nous avons obtenus et les données de la littérature que nous avons colligées montrent bien la complexité de ce phénomène. Si nous avons retrouvé que la composante contractile du strain atrial est bien corrélée à l'existence d'un remodelage ventriculaire au cours du suivi, ce n'est pas le cas pour deux paramètres évaluant la fonction diastolique ventriculaire gauche, la fonction conduit de l'oreillette gauche et le gradient de pression intraventriculaire diastolique. Le taux de néprilysine, endopeptidase clef dans la régulation de plusieurs systèmes neuro-hormonaux est significativement associé au stunning et à la récupération d'une fraction d'éjection ventriculaire gauche au décours de l'infarctus. En revanche, sa quantification – tout comme celle du coenzyme Q10 – n'est pas corrélée à l'existence d'un remodelage ventriculaire gauche. Plus généralement, il existe encore de nombreux points à étudier afin de mieux comprendre le pronostic et les mécanismes physiopathologiques complexes mis en jeu dans la survenue d'un remodelage ventriculaire gauche après un infarctus du myocarde. Il est notamment fondamental que les travaux futurs puissent être menés selon une méthodologie standardisée et dans des populations larges de patients moins sélectionnés.

# Annexes

## **Définition du remodelage ventriculaire gauche en IRM : revue de la littérature**

Ces annexes concernent l'article suivant: **Legallois D**, Hodzic A, Alexandre J, Dolladille C, Saloux E, Manrique A, Roule V, Labombarda F, Milliez P, Beygui F. Definition of left ventricular remodelling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade. Heart Failure Reviews. 2020 ; In press. doi:10.1007/s10741-020-09975-3.

- Données supplémentaires : page 165
- Poster ESC 2020 : page 186

**Definition of left ventricular remodeling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade**

Heart Failure Reviews - Online resource

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**SUPPLEMENTAL MATERIAL**

**Supplementary Methods 1.** Search terms used for MEDLINE

**Supplementary Methods 2.** Modified Newcastle-Ottawa risk of bias scoring guide

**Supplementary Table S1.** PRISMA checklist for the meta-analysis

**Supplementary Table S2.** Characteristics of the studies included in this systematic review

**Supplementary Table S3.** Magnetic resonance imaging data of the studies included in this systematic review

**Supplementary Table S4.** Newcastle-Ottawa risk of bias scores for the non-interventional studies included in this systematic review

**Supplementary Table S5.** Assessment of risk of bias in the randomized controlled trials included in this review, using the Cochrane Collaboration's tool

**Supplementary Table S6.** Sensitivity analysis of the prevalence of left ventricular remodeling among patients with ST-elevation myocardial infarction

**Supplementary Methods 1.** Search terms used for MEDLINE***Acute coronary syndrome***

1. Acute Coronary Syndrome [Mesh]
2. Myocardial infarction
3. OR / 1 – 2

***Time frame***

4. ("2010/01/01"[PDat] : "2019/08/31"[PDat])

***Left ventricular remodeling***

5. remodeling [Title/Abstract]
6. remodelling [Title/Abstract]
7. OR / 5 – 6

***Combined search*** : #3 AND #4 AND #7

**Legend** : MeSH indicates Medical Subject Heading in MEDLINE, PDat indicates publication date.

**Supplementary Methods 2.** Modified Newcastle-Ottawa risk of bias scoring guide.**(1) Sample representativeness:**

1 point: the study population contained consecutive STEMI patients

0 points: the study population contained only specific STEMI patients (e.g., occlusion of the left anterior descending artery or patients with altered left ventricular ejection fraction) or this point is not clearly stated in the manuscript.

**(2) Sample size:**

1 point: sample size was greater than or equal to 100 participants.

0 points: sample size was less than 100 participants.

**(3) Lost to follow-up:**

1 point: more than 70% of included patients were evaluated at the second CMR imaging session

0 points: there was no description of the proportion of patients with two CMR imaging session or less than 70% of patients were evaluated twice

**(4) Ascertainment of left ventricular remodeling:**

1 point: the study employed a commonly used measurement criteria for left ventricular remodeling (e.g., increase of  $\geq 20\%$  of enddiastolic volume between the two CMR imaging sessions)

0 points: the study employed an infrequently used measurement criteria for left ventricular remodeling

**(5) Quality of descriptive statistics reporting:**

1 point: The study reported descriptive statistics to describe the population (e.g., age, left ventricular ejection, culprit vessel) with proper measures of dispersion (e.g., mean, standard deviation or interquartile range for quantitative data).

0 points: The study did not report descriptive statistics, incompletely reported descriptive statistics, or did not report measures of dispersion.

Legend: The individual components listed above are summed to generate a total modified Newcastle-Ottawa risk of bias score for each study. Total scores range from 0 to 5. For the total score grouping, studies were judged to be of low risk of bias ( $\geq 3$  points) or high risk of bias ( $< 3$  points).

Supplementary Table S1. PRISMA checklist for the meta-analysis

| Section/topic                      | #  | Checklist item                                                                                                                                                                                                                                                                                              | Reported section # (top-level heading)                     |
|------------------------------------|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| <b>TITLE</b>                       |    |                                                                                                                                                                                                                                                                                                             |                                                            |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                         | <b>Title</b>                                               |
| <b>ABSTRACT</b>                    |    |                                                                                                                                                                                                                                                                                                             |                                                            |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants; and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | <b>Abstract</b>                                            |
| <b>INTRODUCTION</b>                |    |                                                                                                                                                                                                                                                                                                             |                                                            |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                              | <b>Background</b>                                          |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                  | <b>Background</b>                                          |
| <b>METHODS</b>                     |    |                                                                                                                                                                                                                                                                                                             |                                                            |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                               | <b>Methods, Study Selection</b>                            |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                      | <b>Methods, Data sources and searches, Study Selection</b> |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                  | <b>Methods, Data sources and searches</b>                  |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                               | <b>Methods, Data sources and searches</b>                  |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                   | <b>Methods, Study Selection</b>                            |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                  | <b>Methods, Data extraction and quality assessment</b>     |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                       | <b>Methods, Data extraction and quality assessment</b>     |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                      | <b>Methods, Data extraction and quality assessment</b>     |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                                               | <b>Methods, Data synthesis and analysis</b>                |

|                               |    |                                                                                                                                                                                                          |                                                    |
|-------------------------------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Synthesis of results          | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.                                       | Methods, Data synthesis and analysis               |
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                             | Methods, Data extraction and quality assessment    |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                         | Methods, Data synthesis and analysis               |
| <b>RESULTS</b>                |    |                                                                                                                                                                                                          |                                                    |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                          | Results, Literature search                         |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                             | Table 1, Online Resource                           |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                | Online Resource                                    |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Results, Definition of left ventricular remodeling |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                  | Results, Definition of left ventricular remodeling |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                          | Results, Online Resource                           |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                    | Results, Online Resource                           |
| <b>DISCUSSION</b>             |    |                                                                                                                                                                                                          |                                                    |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                     | Results                                            |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                            | Discussion, Limitations                            |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                  | Discussion                                         |
| <b>FUNDING</b>                |    |                                                                                                                                                                                                          |                                                    |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                               | Source of Funding                                  |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Supplementary Table S2. Characteristics of the studies included in this systematic review

| First author, year    | Sample size | Population                        | Design                                                                                                     | Timing of the second CMR | Definition of LVR                                   | Patients with LVR | Age                                                              | Sex, male                                 | Anterior AMI and/or LAD occlusion      | Revascularization                                                                                          | Pain to balloon, min                                          | Outcomes                                                                          |
|-----------------------|-------------|-----------------------------------|------------------------------------------------------------------------------------------------------------|--------------------------|-----------------------------------------------------|-------------------|------------------------------------------------------------------|-------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Achilli, 2014         | 35          | Anterior STEMI<br>LVEF $\leq$ 45% | RCT (G-CSF)                                                                                                | 6 months                 | $\Delta$ EDV $>$ 20mL<br>or $\Delta$ LVEF $>$ 5%    | NA                | 61 $\pm$ 8 (G-CSF)<br>62 $\pm$ 10 (placebo)                      | 100% (G-CSF)<br>92% (placebo)             | anterior MI :<br>inclusion criteria    | PPCI: inclusion criteria                                                                                   | 277 $\pm$ 166 (G-CSF)<br>238 $\pm$ 129 (placebo)              | Follow-up at 3 years.<br>Relationship with LVR<br>not available                   |
| Biesbroek, 2017       | 42          | STEMI                             | Post-hoc analysis of a<br>prospective study                                                                | 3 months                 | $\Delta$ EDV $\geq$ 15%                             | 8 (19%)           | 60 $\pm$ 9                                                       | 81%                                       | 57%                                    | PPCI: inclusion criteria                                                                                   | 147 $\pm$ 67                                                  | No further follow-up                                                              |
| Bulluck, 2016         | 40          | STEMI                             | Prospective                                                                                                | 5 months                 | $\Delta$ EDV $\geq$ 20%                             | 8 (20%)           | 59 $\pm$ 13                                                      | 88%                                       | 60%                                    | PPCI: inclusion criteria                                                                                   | 267 [122-330]                                                 | No further follow-up                                                              |
| Caldentey, 2017       | 227         | STEMI                             | Prospective                                                                                                | 6 months                 | $\Delta$ EDV $\geq$ 20%                             | 29 (16%)          | 58 $\pm$ 12 (LVR)<br>59 $\pm$ 11 (No LVR)                        | 93% (LVR)<br>83% (No LVR)                 | 43%                                    | PCI: inclusion criteria<br>Complete revascularization: 79%<br>(LVR) and 70% (No LVR)                       | 217 $\pm$ 168 (LVR)<br>268 $\pm$ 315 (No LVR)                 | Follow-up: 79 $\pm$ 49<br>months.<br>Relationship with LVR<br>not available       |
| Carberry, 2017        | 283         | STEMI                             | Prospective                                                                                                | 6 months                 | $\Delta$ EDV $\geq$ 20%                             | 32 (11.3%)        | 59 $\pm$ 11                                                      | 75%                                       | 37%                                    | PPCI: 94% Rescue PCI: 4%<br>Successful fibrinolysis: 2%                                                    | 248 $\pm$ 207                                                 | Median follow-up 1330<br>days. Relationship with<br>LVR not available             |
| Cha, 2019             | 82          | STEMI                             | Retrospective                                                                                              | 6.5 months               | $\Delta$ EDV $\geq$ 20%                             | 20 (24.4%)        | 59.2 $\pm$ 11.1                                                  | 89%                                       | not precisely described<br>>53.6%      | not available                                                                                              | 322 $\pm$ 336 (LVR)<br>566 $\pm$ 1644 (no LVR)                | No further follow-up                                                              |
| Eitel, 2011           | 112         | STEMI                             | RCT (intracoronary vs.<br>intravenous<br>abiximab)                                                         | 6 months                 | $\Delta$ ESVI $>$ 0%                                | 51 (45.5%)        | 64 [54-70] (IC<br>abiximab)<br>66 [54-73] (IV<br>abiximab)       | 82% (IC abiximab)<br>77% (IV abiximab)    | 57% (IC abiximab)<br>52% (IV abiximab) | PPCI: inclusion criteria                                                                                   | 244 [163-433] (IC<br>abix.)<br>218 [159-323] (IV<br>abix.)    | No further follow-up                                                              |
| Fabregat-Andrés, 2015 | 31          | Anterior STEMI                    | Prospective (PGC-1 $\alpha$<br>induction)                                                                  | 6 months                 | $\Delta$ EDV $>$ 10%                                | 15 (48%)          | 57.2 $\pm$ 10.6 (induction)<br>60.1 $\pm$ 13.9 (no<br>induction) | 62.5% (induction)<br>91.3% (no induction) | anterior MI :<br>inclusion criteria    | PPCI/Rescue PCI:<br>37.5%/62.5% (PGC-1 $\alpha$<br>induction) 60.9%/39.1% (No<br>PGC-1 $\alpha$ induction) | 283 $\pm$ 192 (induction)<br>202 $\pm$ 154 (no<br>induction)  | No further follow-up                                                              |
| Garcia, 2019          | 192         | STEMI                             | Prospective                                                                                                | 3 months<br>12 months    | $\Delta$ ESV $\geq$ 10%                             | 32 (16.7%)        | 58 $\pm$ 9                                                       | 81%                                       | 53%                                    | PPCI: inclusion criteria                                                                                   | 293 $\pm$ 130                                                 | No further follow-up                                                              |
| Garg, 2017            | 50          | STEMI                             | Prospective (increase<br>in average normal<br>myocardial extra-<br>cellular volume at<br>follow-up or not) | 3 months                 | $\Delta$ ESV $>$ 15%                                | 10 (20%)          | 58 $\pm$ 11 (increase)<br>60 $\pm$ 11 (no increase)              | 84%                                       | 60%                                    | PPCI: inclusion criteria                                                                                   | 222 [149-344]<br>(increase)<br>261 [158-454] (no<br>increase) | No further follow-up                                                              |
| Gerbaud, 2014         | 124         | STEMI                             | Prospective                                                                                                | 3 months                 | $\Delta$ ESV $\geq$ 15%                             | 34 (27.4%)        | 56.7 $\pm$ 11.7<br>(ivabradine)<br>58.2 $\pm$ 10.5 (control)     | 90.3% (ivabradine)<br>88.7% (control)     | 46.8% (ivabradine)<br>43.5% (control)  | PPCI: inclusion criteria                                                                                   | 294 $\pm$ 182 (ivabradine)<br>291 $\pm$ 169 (control)         | No further follow-up                                                              |
| Gohbara, 2015         | 69          | STEMI                             | Prospective                                                                                                | 7 months                 | $\Delta$ EDVI $\geq$ 20%                            | 18 (26%)          | 63 $\pm$ 13                                                      | 86%                                       | 51%                                    | not available                                                                                              | 210 $\pm$ 144                                                 | No further follow-up                                                              |
| Grabmaier, 2017       | 44          | STEMI                             | Post-hoc analysis of a<br>RCT (sitagliptin and G-<br>CSF)                                                  | 6 months                 | $\Delta$ EDV<br>(continuous)                        | NA                | 56 [48-66]                                                       | 84.1%                                     | non available                          | PCI: inclusion criteria                                                                                    | 366 $\pm$ 300                                                 | Long-term follow-up<br>available but<br>relationship with LVR is<br>not described |
| Hallen, 2010          | 132         | STEMI                             | Post-hoc analysis of a<br>RCT (FX06)                                                                       | 4 months                 | $\Delta$ ESVI and<br>$\Delta$ EDVI<br>(continuous)  | NA                | 58.9 $\pm$ 11.2                                                  | 76%                                       | 47%                                    | PPCI: inclusion criteria                                                                                   | 195 $\pm$ 85                                                  | No further follow-up                                                              |
| Husser, 2013          | 234         | STEMI                             | Prospective                                                                                                | 6 months                 | dilated ESVI<br>according to<br>reference<br>values | 94 (40%)          | 57 $\pm$ 12 (LVR)<br>58 $\pm$ 11 (no LVR)                        | 83% (LVR)<br>82% (no LVR)                 | 66% (LVR)<br>48% (no LVR)              | PPCI: 35% Thrombolysis: 53%<br>Rescue PCI: 13%                                                             | 265 $\pm$ 176 (LVR)<br>226 $\pm$ 164 (no LVR)                 | Median follow-up 140<br>weeks. Relationship<br>with LVR not available             |

| First author, year        | Sample size | Population | Design                                                                  | Timing of the second CMR | Definition of LVR                                                       | Patients with LVR | Age                                                | Sex, male                                | Anterior AMI and/or LAD occlusion        | Revascularization                                                     | Pain to balloon, min                                         | Outcomes                                                                                                                                     |
|---------------------------|-------------|------------|-------------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------|-------------------|----------------------------------------------------|------------------------------------------|------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Hutlin, 2017              | 121         | STEMI      | Prospective                                                             | 6 months                 | $\Delta\text{EDV} > 17\text{mL}$                                        | 36 (29.8)         | 56 ± 10                                            | 85%                                      | 54%                                      | PPCI: inclusion criteria                                              | 258 ± 138                                                    | No further follow-up                                                                                                                         |
| Janssens, 2018            | 197         | STEMI      | RCT (inhaled nitric oxide)                                              | 4 months                 | $\Delta\text{ESV}$ and $\Delta\text{EDV}$ (continuous and binary index) | NA                | 63 ± 13 (inhaled nitric oxide) 60 ± 11 (control)   | 64% (inhaled nitric oxide) 74% (control) | 43% (inhaled nitric oxide) 45% (control) | PPCI: inclusion criteria                                              | 222 [162-356] (inhaled nitric oxide) 210 [156-356] (control) | One year follow-up but relationship with LVR is not described                                                                                |
| Mangion, 2016             | 72          | STEMI      | Post-hoc analysis of a RCT (culprit-artery PCI only vs. preventive PCI) | 7 months                 | $\Delta\text{ESVI} \geq 20\%$ and $\Delta\text{EDVI} \geq 20\%$         | 11 (13%)          | 60 [39-83] (culprit only) 61 [38-88] (preventive)  | 81% (culprit only) 74% (preventive)      | 55% (culprit only) 24% (preventive)      | PPCI: inclusion criteria                                              | 174 [129-413] (culprit only) 177 [123-326] (preventive)      | No further follow-up                                                                                                                         |
| Mele, 2017                | 41          | STEMI      | Retrospective                                                           | 6 months                 | $\Delta\text{EDV} \geq 15\%$                                            | 10 (24%)          | 55.4 ± 9.1 (LVR) 61.2 ± 11.2 (No LVR)              | 90% (LVR) 87% (no LVR)                   | 60% (LVR) 61% (No LVR)                   | myocardial revascularization within 90 min from the onset of symptoms | < 90 min (inclusion criteria)                                | No further follow-up                                                                                                                         |
| Najjar, 2011              | 124         | STEMI      | RCT (erythropoietin (EPO))                                              | 3 months                 | $\text{EDVI}$ , $\text{ESVI}$ and $\text{LV mass}$ index (continuous)   | NA                | 55.6 ± 12.6 (EPO) 57.4 ± 11.9 (placebo)            | 89.7% (EPO) 80% (placebo)                | 29.4% (EPO) 27.1% (placebo)              | PPCI/Rescue PCI: 94.1%/5.9% (EPO) 78.6%/21.4% (placebo)               | 210.9 ± 98.3 (EPO) 201.9 ± 111.2 (placebo)                   | No further follow-up                                                                                                                         |
| O'Regan, 2012             | 46          | STEMI      | Prospective                                                             | 12 months                | $\Delta\text{EDV} \geq 20\%$                                            | 16 (35%)          | 55 ± 10                                            | 96%                                      | 54%                                      | PPCI: inclusion criteria                                              | 210 ± 156                                                    | No further follow-up                                                                                                                         |
| Pokorney, 2012            | 66          | STEMI      | Prospective                                                             | 4 months 14 months       | $\Delta\text{EDVI} > 20\%$                                              | 12 (18%)          | 58 ± 11                                            | 91%                                      | 56%                                      | PPCI: inclusion criteria                                              | not available                                                | No further follow-up                                                                                                                         |
| Reindl, 2018              | 102         | STEMI      | Prospective                                                             | 4 months                 | $\Delta\text{EDV} \geq 20\%$                                            | 15 (14.7%)        | 56 [46-65]                                         | 89%                                      | 42%                                      | PPCI: inclusion criteria                                              | 194 [137-337]                                                | LVR showed a significant association with lower event-free survival (events: 3%, median follow-up: 367 days)                                 |
| Reinstadler, 2013         | 47          | STEMI      | Prospective                                                             | 4 months                 | $\Delta\text{EDV} \geq 20\%$                                            | 6 (13%)           | 57 ± 10                                            | 85.2%                                    | 40.7%                                    | PPCI: inclusion criteria                                              | not available                                                | No further follow-up                                                                                                                         |
| Rodriguez-Palomares, 2019 | 374         | STEMI      | Variable                                                                | 6 months                 | $\Delta\text{EDV} > 15\%$                                               | 105 (28.1%)       | 59.2 ± 12                                          | 83.4%                                    | 56.4%                                    | 67.1% (acute phase)                                                   | not available                                                | The primary endpoint (cardiovascular mortality, hospitalization for heart failure or ventricular arrhythmia) occurred in 49 patients (13.1%) |
| Shetelig, 2018            | 240         | STEMI      | Post-hoc analysis of a RCT (ischemic postconditioning)                  | 4 months                 | increase $\text{EDVI} \geq 10\text{mL/m}^2$                             | not available     | 60 [53-77]                                         | 82.2%                                    | 48.8%                                    | PPCI: inclusion criteria                                              | 187 [125-265]                                                | Adverse clinical event at 12 months and vital status at 70 months. Relationship with LVR not available                                       |
| Shetty, 2017              | 65          | STEMI      | Prospective                                                             | 4 months                 | $\Delta\text{ESVI} \geq 15\%$ or $\Delta\text{EDVI} \geq 20\%$          | 11 (16.9%)        | 59.5 ± 11.0                                        | 92%                                      | 46%                                      | PPCI: 60% Thrombolysis: 20% Rescue PCI: 12% Late PCI: 8%              | not available                                                | No further follow-up                                                                                                                         |
| Sörensson, 2013           | 68          | STEMI      | Post-hoc analysis of a RCT (Postconditioning)                           | 3 months 12 months       | $\Delta\text{ESV} \geq 15\%$                                            | 9 (13%)           | 63 [37-85] (postconditioning) 62 [42-85] (control) | 85% (postconditioning) 89% (control)     | 33% (postconditioning) 37% (control)     | PPCI: inclusion criteria                                              | 165 [133-202] (postconditioning) 180 [141-255] (control)     | No further follow-up                                                                                                                         |
| Sugano, 2017              | 68          | STEMI      | Prospective                                                             | 6 months                 | $\Delta\text{EDV} > 5\%$                                                | 22 (32%)          | 62.2 ± 14.3 (LVR) 63.8 ± 12.5 (No LVR)             | 84% (LVR) 69% (No LVR)                   | 57% (LVR) 49% (No LVR)                   | PPCI: inclusion criteria                                              | 360 [180-540] (LVR) 180 [120-288] (No LVR)                   | No further follow-up                                                                                                                         |

| First author, year | Sample size | Population       | Design                                                        | Timing of the second CMR | Definition of LVR                  | Patients with LVR | Age                                                                               | Sex, male                                                                 | Anterior AMI and/or LAD occlusion                                         | Revascularization                                                | Pain to balloon, min                                                                  | Outcomes                                                                          |
|--------------------|-------------|------------------|---------------------------------------------------------------|--------------------------|------------------------------------|-------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Surder, 2016       | 150         | STEMI LVEF < 45% | Post-hoc analysis of a RCT (Intracoronary delivery of BM-MNC) | 12 months                | EDV, ESV (continuous)              | NA                | 56 ± 14.5 (control)<br>55 ± 15 (early BM-MNC)<br>62 ± 15 (late BM-MNC)            | 83.6% (control)<br>86.2% (early BM-MNC)<br>82.5% (late BM-MNC)            | 89% (control)<br>95% (early BM-MNC)<br>92% (late BM-MNC)                  | PPCI 94% (control)<br>98.5% (early BM-MNC)<br>100% (late BM-MNC) | 270 ± 300 (control)<br>288 ± 324 (early BM-MNC)<br>240 ± 288 (late BM-MNC)            | Median follow-up: 38 months. Relationship between events and LVR is not described |
| Symons, 2016       | 383         | STEMI            | Prospective                                                   | 4 months                 | $\Delta$ EDV > 20%                 | 78 (20.4%)        | 60.0 ± 11.6                                                                       | 83%                                                                       | 50%                                                                       | PPCI: inclusion criteria                                         | 196 [140-295]                                                                         | No further follow-up                                                              |
| Tanimoto, 2010     | 104         | STEMI            | Prospective                                                   | 8 months                 | $\Delta$ EDV > 15%                 | 21 (20%)          | 64 ± 13 (papillary muscle infarction)<br>65 ± 12 (no papillary muscle infarction) | 83% (papillary muscle infarction)<br>68% (no papillary muscle infarction) | 13% (papillary muscle infarction)<br>55% (no papillary muscle infarction) | PPCI: inclusion criteria                                         | 318 ± 210 (papillary muscle infarction)<br>300 ± 216 (no papillary muscle infarction) | No further follow-up                                                              |
| Traverse, 2010     | 40          | Anterior STEMI   | RCT (stem cells)                                              | 6 months                 | AESV and $\Delta$ EDV (continuous) | NA                | 52.5 [43-64] (BMC)<br>57.5 [54-59] (placebo)                                      | 83.3% (BMC)<br>60% (placebo)                                              | anterior MI : Inclusion criteria                                          | PPCI: inclusion criteria                                         | 276 [120-720] (BMC)<br>174 [168-636] (placebo)                                        | No further follow-up                                                              |
| Van Melle, 2010    | 50          | STEMI            | Prospective                                                   | 4 months                 | $\Delta$ ESV ≥ 15%                 | 9 (18%)           | 55.1 ± 9.2                                                                        | 86%                                                                       | 52%                                                                       | PPCI: inclusion criteria                                         | not available                                                                         | No further follow-up                                                              |
| Waiaabe, 2016      | 92          | STEMI            | Prospective (heterogeneous enhancement (HE))                  | 6 months                 | $\Delta$ ESV > 0%                  | 29 (32%)          | 66 ± 12 (HE (-))<br>58 ± 12 (HE (+))                                              | 81% (HE (-))<br>88% (HE (+))                                              | 49% (HE (-))<br>64% (HE (+))                                              | not available                                                    | 384 ± 384 (HE (-))<br>444 ± 390 (HE (+))                                              | No further follow-up                                                              |
| Wong, 2013         | 64          | STEMI            | Prospective                                                   | 3 months                 | EDV (continuous)                   | NA                | 61 ± 10                                                                           | 83%                                                                       | 41%                                                                       | PPCI: inclusion criteria                                         | 192 [147-279]                                                                         | No further follow-up                                                              |
| Yoon, 2013         | 84          | STEMI            | RCT (PCI with distal protection)                              | 6 months                 | $\Delta$ EDV > 20%                 | 17 (20%)          | 58 ± 12 (distal protection)<br>58 ± 11 (control)                                  | 80% (distal protection)<br>78.7% (control)                                | 54% (distal protection)<br>56% (control)                                  | PPCI: inclusion criteria                                         | 291 ± 133 (distal protection)<br>309 ± 157 (control)                                  | No further follow-up                                                              |

AMI, acute myocardial infarction; BMC, bone marrow-derived cells; BM-MNC, bone marrow-derived mononuclear cells; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EPO, erythropoietin; ESV, end-systolic volume; ESVI, end-systolic volume index; G-CSF, granulocyte-colony-stimulating factor; HE, heterogeneous enhancement; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; LVR, left ventricular remodeling; PCI, percutaneous coronary intervention; PGC-1  $\alpha$ , Peroxisome proliferator-activated receptor gamma coactivator 1  $\alpha$ ; PPCI, primary percutaneous coronary intervention; RCT, randomized clinical trial; STEMI, ST-elevation myocardial infarction; Values are expressed as mean ± standard deviation or median [interquartile range].

Supplementary Table 3. Magnetic resonance imaging data of the studies included in this systematic review

| First author, Sample year | Sample size | Infarct size                                                                             | Initial LV volumes                                                                                                                                          | Initial LVEF, %                                                                                      | LV volumes at follow-up                                                                                                                                                                                                                                                                                               | LVEF at follow-up                                                                                                                                |
|---------------------------|-------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Achilli, 2014             | 35          | 4.2 ± 3.0 transmural LGE segments (G-CSF)<br>4.1 ± 2.8 transmural LGE segments (placebo) | EDV: 144.3 ± 33 (G-CSF)<br>ESV: 76.1 ± 27.1 (G-CSF)<br>EDV: 147.1 ± 42.8 (placebo)<br>ESV: 79.0 ± 33.3 (placebo)                                            | 47.8 ± 10.9 (G-CSF)<br>47.3 ± 8.5 (placebo)                                                          | EDV: 145.1 ± 33.9 (G-CSF)<br>ESV: 76.3 ± 25.4 (G-CSF)<br>EDV: 166.7 ± 43.7 (placebo)<br>ESV: 86.5 ± 35.7 (placebo)                                                                                                                                                                                                    | 48.0 ± 10.0 (G-CSF)<br>49.3 ± 9.2 (placebo)                                                                                                      |
| Biesbroek, 2017           | 42          | 16% [8-26]                                                                               | EDV: 183 ± 35<br>ESV: 91 ± 28                                                                                                                               | 51 ± 8                                                                                               | EDV: 189 ± 45<br>ESV: 95 ± 39                                                                                                                                                                                                                                                                                         | 52 ± 10                                                                                                                                          |
| Bulluck, 2016             | 40          | 27.4% ± 14.6%                                                                            | EDV: 172 ± 38<br>ESV: 90 ± 30                                                                                                                               | 49 ± 8                                                                                               | EDV: 182 ± 49<br>ESV: 88 ± 38                                                                                                                                                                                                                                                                                         | 53 ± 10                                                                                                                                          |
| Caldentey, 2017           | 227         | 23.4% ± 15.9% (LVR)<br>16.2% ± 11.1% (No LVR)                                            | EDV: 77.5 ± 21.3 (LVR)<br>ESV: 45.2 ± 20.3 (LVR)<br>EDV: 83.6 ± 15.2 (No LVR)<br>ESV: 43.1 ± 12.5 (No LVR)                                                  | 44 ± 13 (LVR)<br>49 ± 8 (No LVR)                                                                     | EDV: 105.0 ± 29.6 (LVR)<br>ESV: 60.3 ± 31.4 (LVR)<br>EDV: 80.9 ± 15.4 (No LVR)<br>ESV: 37.7 ± 11.7 (No LVR)                                                                                                                                                                                                           | 46 ± 14 (LVR)<br>54 ± 7 (No LVR)                                                                                                                 |
| Carberry, 2017            | 283         | 18% ± 13%                                                                                | EDV: 161 ± 31 (men)<br>ESV: 74 ± 26 (men)<br>EDV: 124 ± 25 (women)<br>ESV: 54 ± 18 (women)                                                                  | 55.3                                                                                                 | EDV: 169 ± 42 (men)<br>ESV: 68 ± 35 (men)<br>EDV: 127 ± 30 (women)<br>ESV: 46 ± 18 (women)                                                                                                                                                                                                                            | 62 ± 9                                                                                                                                           |
| Cha, 2019                 | 82          | 27.3% ± 15.1% (LVR)<br>19.2% ± 10.6% (no LVR)                                            | 125.8 ± 35.0 (LVR)<br>141.6 ± 29.9 (no LVR)                                                                                                                 | 50.9 ± 12.0 (LVR)<br>55.3 ± 9.3 (no LVR)                                                             | not available                                                                                                                                                                                                                                                                                                         | not available                                                                                                                                    |
| Eitel, 2011               | 112         | 18.2% ± 14.8% (IC abciximab)<br>25.0% ± 13.9% (IV abciximab)                             | EDV: 80.0 ± 16.8 (IC abciximab)<br>ESV: 45.8 ± 17.1 (IC abciximab)<br>EDV: 78.4 ± 16.9 (IV abciximab)<br>ESV: 44.1 ± 15.2 (IV abciximab)                    | 44.0 ± 10.6 (IC abciximab)<br>45.4 ± 10.2 (IV abciximab)                                             | EDV: 80.8 ± 21.8 (IC abciximab)<br>ESV: 42.7 ± 21.3 (IC abciximab)<br>EDV: 78.9 ± 22.7 (IV abciximab)<br>ESV: 44.3 ± 20.8 (IV abciximab)                                                                                                                                                                              | 48.1 ± 12.1 (IC abciximab)<br>46.8 ± 11.6 (IV abciximab)                                                                                         |
| Fabregat-Andrés, 2015     | 31          | 20.9% ± 7.9% PGC-1 $\alpha$ induction)<br>16.9% ± 11.8% (No PGC-1 $\alpha$ induction)    | EDV: 92.3 ± 6.2 (PGC-1 $\alpha$ induction and/or microvascular obstruction)<br>EDV: 91.0 ± 11.3 (No PGC-1 $\alpha$ induction, no microvascular obstruction) | 50.1 ± 2.1 (PGC-1 $\alpha$ induction and/or MVO)<br>49.1 ± 2.9 (No PGC-1 $\alpha$ induction, no MVO) | EDV: 102.0 ± 7.7 (PGC-1 $\alpha$ induction and/or microvascular obstruction)<br>EDV: 81.0 ± 6.2 (No PGC-1 $\alpha$ induction, no microvascular obstruction)                                                                                                                                                           | 49.1 ± 2.1 (PGC-1 $\alpha$ induction and/or microvascular obstruction)<br>57.0 ± 3.2 (No PGC-1 $\alpha$ induction, no microvascular obstruction) |
| García, 2019              | 192         | 20% ± 14.4% (LVR)<br>15.8% ± 10.0% (No LVR)                                              | EDV: 91.3 ± 22.4 (LVR)<br>ESV: 46.8 ± 17.5 (LVR)<br>EDV: 94.7 ± 14.8 (No LVR)<br>ESV: 49.6 ± 12.2 (No LVR)                                                  | 48.6 ± 10.1 (LVR)<br>47.7 ± 9.0 (No LVR)                                                             | EDV: 99.3 ± 25.2 (LVR – 3 months)<br>ESV: 53.1 ± 22.1 (LVR – 3 months)<br>EDV: 88.8 ± 16.2 (No LVR – 3 months)<br>ESV: 42.1 ± 13.5 (No LVR – 3 months)<br>EDV: 106.2 ± 27.6 (LVR – 12 months)<br>ESV: 57.2 ± 25.0 (LVR – 12 months)<br>EDV: 86.6 ± 17.9 (No LVR – 12 months)<br>ESV: 40.9 ± 14.5 (No LVR – 12 months) | 48.6 ± 10.4 (LVR – 3 months)<br>53.1 ± 8.6 (No LVR – 3 months)<br>47.3 ± 9.9 (LVR – 12 months)<br>53.5 ± 8.9 (No LVR – 12 months)                |
| Garg, 2017                | 50          | 23.9% [17-38]                                                                            | EDV: 79.1 [71-87]<br>ESV: 42 [36-50]                                                                                                                        | 45.65 [36-51]                                                                                        | EDV: 80.45 [70-89]<br>ESV: 38.7 [31-47]                                                                                                                                                                                                                                                                               | 52.35 [43-59]                                                                                                                                    |

|                           |     |                                                                        |                                                                                                                                                              |                                                                          |                                                                                                                                                              |                                                                  |
|---------------------------|-----|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| Gerbaud, 2014             | 124 | 16.3% ± 7.5% (ivabradine)<br>15.6% ± 6.8% (control)                    | EDVI: 72.5 ± 14.6 (ivabradine)<br>ESVI: 31.0 ± 11.1 (ivabradine)<br>EDVI: 72.3 ± 16.1 (control)<br>ESVI: 32.0 ± 10.4 (control)                               | 57.9 ± 9.8 (ivabradine)<br>56.4 ± 9.1 (control)                          | EDVI: 75.0 ± 18.5 (ivabradine)<br>ESVI: 31.0 ± 14.4 (ivabradine)<br>EDVI: 78.5 ± 18.0 (control)<br>ESVI: 35.3 ± 14.3 (control)                               | 60.0 ± 10.4 (ivabradine)<br>56.5 ± 10.6 (control)                |
| Gohbara, 2015             | 69  | not available                                                          | EDVI: 78 ± 20                                                                                                                                                | 46 ± 11                                                                  | EDVI: 80 ± 20                                                                                                                                                | 47 ± 9                                                           |
| Grabmaier, 2017           | 44  | non available                                                          | non available                                                                                                                                                | non available                                                            | non available                                                                                                                                                | non available                                                    |
| Hallen, 2010              | 132 | not available                                                          | mean EDVI: 76.1<br>mean ESVI: 41                                                                                                                             | mean LVEF: 46.6%                                                         | mean EDVI: 80.2<br>mean ESVI: 42.4                                                                                                                           | mean LVEF: 48.5%                                                 |
| Husser, 2013              | 234 | 22% ± 16%                                                              | EDVI: 94 ± 26 (LVR)<br>ESVI: 54 ± 22 (LVR)<br>EDVI: 70 ± 16 (no LVR)<br>ESVI: 29 ± 10 (no LVR)                                                               | 43 ± 10 (LVR)<br>58 ± 10 (no LVR)                                        | not available                                                                                                                                                | not available                                                    |
| Huittin, 2017             | 121 | 16% ± 13%                                                              | EDVI: 92 ± 15                                                                                                                                                | 42 ± 8                                                                   | EDVI: 96 ± 18                                                                                                                                                | 49 ± 9                                                           |
| Janssens, 2018            | 197 | 18% ± 13% (inhaled nitric oxide)<br>19% ± 15% (control)                | EDV: 79 ± 16 (inhaled nitric oxide)<br>ESV: 41 ± 14 (inhaled nitric oxide)<br>EDV: 82 ± 19 (control)<br>ESV: 44 ± 18 (control)                               | 49 ± 11 (inhaled nitric oxide)<br>47 ± 10 (control)                      | EDV: 84 ± 18 (inhaled nitric oxide)<br>ESV: 41 ± 16 (inhaled nitric oxide)<br>EDV: 90 ± 22 (control)<br>ESV: 46 ± 21 (control)                               | 53 ± 10 (inhaled nitric oxide)<br>51 ± 10 (control)              |
| Mangion, 2016             | 72  | 18.12% ± 13.85% (culprit only PCI)<br>14.83% ± 11.75% (preventive PCI) | EDVI: 64.8 [57.1-77.4] (culprit only)<br>ESVI: 33.5 [27.3-47.8] (culprit only)<br>EDVI: 68.5 [54.7-79.0] (preventive)<br>ESVI: 34.1 [25.5-49.1] (preventive) | 47.9 [40.3-47.9] (culprit only PCI)<br>48.5 [38.6-55.8] (preventive PCI) | EDVI: 69.3 [59.4-79.9] (culprit only)<br>ESVI: 31.8 [24.4-43.0] (culprit only)<br>EDVI: 66.1 [54.7-73.7] (preventive)<br>ESVI: 30.7 [23.0-36.3] (preventive) | 51.7 [42.9-60.2] (culprit only)<br>54.4 [49.3-62.8] (preventive) |
| Mele, 2017                | 41  | non available                                                          | EDV: 145.1 ± 29.3 (LVR)<br>ESV: 90.6 ± 26.4 (LVR)<br>EDV: 154.9 ± 36.2 (No LVR)<br>ESV: 81.2 ± 28.5 (No LVR)                                                 | 38.4 ± 6.9 (LVR)<br>48.6 ± 8.0 (No LVR)                                  | EDV: 185.9 ± 49.8 (LVR)<br>ESV: 114.7 ± 44.3 (LVR)<br>EDV: 151.8 ± 39.9 (No LVR)<br>ESV: 74.0 ± 31.3 (No LVR)                                                | 39.9 ± 7.5 (LVR)<br>52.5 ± 8.2 (No LVR)                          |
| Najjar, 2011              | 124 | 10.6% ± 8.6% (EPO)<br>10.4% ± 7.6% (placebo)                           | EDVI: 65.6 ± 18.2 (EPO)<br>ESVI: 34.7 ± 14.7 (EPO)<br>EDVI: 63.4 ± 15.4 (placebo)<br>ESVI: 32.6 ± 10.6 (placebo)                                             | 48.2 ± 9.1 (EPO)<br>48.9 ± 8.7 (placebo)                                 | EDVI: 70.0 ± 17.1 (EPO)<br>ESVI: 34.1 ± 14.0 (EPO)<br>EDVI: 66.6 ± 19.1 (placebo)<br>ESVI: 32.0 ± 11.7 (placebo)                                             | 52.2 ± 9.3 (EPO)<br>52.0 ± 8.8 (placebo)                         |
| O'Regan, 2012             | 46  | 13.3% (range 1.2 – 34.0%)                                              | EDV: 146 ± 38<br>ESV: 67 ± 26                                                                                                                                | 56 ± 9                                                                   | EDV: 160 ± 46<br>ESV: 71 ± 31                                                                                                                                | 57 ± 12                                                          |
| Pokorney, 2012            | 66  | 21% ± 13%                                                              | EDVI: 79 ± 17                                                                                                                                                | 42 ± 10                                                                  | EDVI: 82 ± 18 (4 months)<br>EDVI: 82 ± 20 (14 months)                                                                                                        | 46 ± 10 (4 months)<br>46 ± 11 (14 months)                        |
| Reindl, 2018              | 102 | 16% [8-25]                                                             | EDV: 150 [127-167]<br>ESV: 64 [51-82]                                                                                                                        | 55 [48-61]                                                               | EDV: 154 [131-172]<br>ESV: 58 [49-77]                                                                                                                        | 60 [53-66]                                                       |
| Reinstadler, 2013         | 47  | 18% ± 10%                                                              | EDV: 144 ± 27<br>ESV: 66 ± 22                                                                                                                                | 55 ± 10                                                                  | EDV: 148 ± 29<br>ESV: 60 ± 25                                                                                                                                | 61 ± 10                                                          |
| Rodriguez-Palomares, 2019 | 374 | 21.9% ± 14.3%                                                          | EDVI: 79.7 ± 21.9<br>ESVI: 39.6 ± 18.8                                                                                                                       | 51.6 ± 12.0                                                              | EDV: 82 ± 26<br>ESV: 39 ± 23                                                                                                                                 | 55 ± 12                                                          |

|                     |     |                                                                                               |                                                                                                                                                                                  |                                                                               |                                                                                                                                                                                   |                                                                                  |
|---------------------|-----|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Shetelig,<br>2018   | 240 | 15.1% [9.7-22.5] (IL-8 ≤ median)<br>23.8% [12.7-34.6] (IL-8 > median)                         | not available                                                                                                                                                                    | 52 [47-59] IL-8 ≤ median<br>48 [38-56] IL-8 > median                          | not available                                                                                                                                                                     | 58% [52-63] IL-8 ≤ median<br>52% [42-61] IL-8 > median                           |
| Shetye,<br>2017     | 65  | 22.3% [14.5-35.5]                                                                             | EDVI: 91.1 [84.5-102.2]<br>ESVI: 53.5 [47.6-65.9]                                                                                                                                | 41.0 ± 8.4                                                                    | EDVI: 93.5 [85-106]<br>ESVI: 47.7 [39.8-61.6]                                                                                                                                     | 47.2 ± 8.46                                                                      |
| Sörensson<br>, 2013 | 68  | 9.9% [5.5-14.9] (postconditioning)<br>8.0% [5.5-14.1] (control)                               | EDVI: 79 [73-84] (postconditioning)<br>ESVI: 43 [36-55] (postconditioning)<br>EDVI: 89 [80-99] (control)<br>ESVI: 49 [37-56] (control)                                           | not available                                                                 | EDVI: 79 [73-91] (postconditioning)<br>ESVI: 40 [32-48] (postconditioning)<br>EDVI: 86 [70-104] (control)<br>ESVI: 39 [33-57] (control)                                           | not available                                                                    |
| Sugano,<br>2017     | 68  | 3.6 ± 2.8 transmural infarct segments (LVR)<br>2.7 ± 2.5 transmural infarct segments (No LVR) | EDVI: 109.2 ± 37.0 (LVR)<br>ESV: 63.1 ± 32.4 (LVR)<br>EDV: 121.7 ± 35.1 (No LVR)<br>ESV: 67.7 ± 28.9 (No LVR)                                                                    | 43.6 ± 10.4 (LVR)<br>45.7 ± 9.6 (No LVR)                                      | EDVI: 134.9 ± 41.9 (LVR)<br>ESV: 71.6 ± 33.4 (LVR)<br>EDV: 105.4 ± 34.1 (No LVR)<br>ESV: 51.9 ± 24.0 (No LVR)                                                                     | 47.9 ± 9.7 (LVR)<br>52.9 ± 10.4 (No LVR)                                         |
| Sürder,<br>2016     | 150 | 28.3% ± 16.3% (control)<br>28.1% ± 16.2% (early BM-MNC)<br>26.6% ± 15.9% (late BM-MNC)        | EDVI: 153 ± 38 (control)<br>ESV: 94 ± 33 (control)<br>EDV: 156 ± 41 (early BM-MNC)<br>ESV: 100 ± 36 (early BM-MNC)<br>EDV: 157 ± 37 (late BM-MNC)<br>ESV: 100 ± 29 (late BM-MNC) | 40.0 ± 9.9 (control)<br>36.5 ± 9.9 (early BM-MNC)<br>36.3 ± 8.2 (late BM-MNC) | EDVI: 170 ± 56 (control)<br>ESV: 110 ± 53 (control)<br>EDV: 179 ± 61 (early BM-MNC)<br>ESV: 118 ± 56 (early BM-MNC)<br>EDV: 164 ± 47 (late BM-MNC)<br>ESV: 107 ± 44 (late BM-MNC) | 38.1 ± 13.6 (control)<br>36.2 ± 11.4 (early BM-MNC)<br>36.6 ± 12.2 (late BM-MNC) |
| Symons,<br>2016     | 383 | 16.7 ± 12.8                                                                                   | EDVI: 78.3 ± 18.5<br>ESVI: 40.1 ± 14.5                                                                                                                                           | 49.5 ± 9.9                                                                    | EDVI: 82.5 ± 21.4<br>ESVI: 40.7 ± 16.8                                                                                                                                            | 51.8 ± 10.3                                                                      |
| Tanimoto,<br>2010   | 104 | 21% ± 8% (mitral regurgitation)<br>16% ± 11% (no mitral regurgitation)                        | EDV: 130 ± 33 (mitral regurgitation)<br>ESV: 71 ± 28 (mitral regurgitation)<br>EDV: 116 ± 29 (no mitral regurgitation)<br>ESV: 60 ± 25 (no mitral regurgitation)                 | 47 ± 10 (mitral regurgitation)<br>50 ± 10 (no mitral regurgitation)           | not available                                                                                                                                                                     | not available                                                                    |
| Traverse,<br>2010   | 40  | not available                                                                                 | EDV: 88 ± 31 (BMC)<br>ESV: 46 ± 26 (BMC)<br>EDV: 77 ± 12 (placebo)<br>ESV: 40 ± 11 (placebo)                                                                                     | 49.0 ± 9.5 (BMC)<br>48.6 ± 8.5 (placebo)                                      | ΔEDV: -4 ± 22 (BMC)<br>ΔESV: -7 ± 3.3 (BMC)<br>ΔEDV: 17 ± 11 (placebo)<br>ΔESV: -2 ± 8.4 (placebo)                                                                                | 55.1 ± 9.6 (BMC)<br>56.7 ± 13.9 (placebo)                                        |
| Van Melle,<br>2010  | 50  | not available                                                                                 | not available                                                                                                                                                                    | 42 ± 9                                                                        | not available                                                                                                                                                                     | 47 ± 10                                                                          |
| Watabe,<br>2016     | 92  | not available                                                                                 | EDV: 119 ± 31 (HE (-))<br>ESV: 67 ± 25 (HE (-))<br>EDV: 143 ± 38 (HE (+))<br>ESV: 90 ± 33 (HE (+))                                                                               | 45 ± 9 (HE (-))<br>38 ± 8 (HE (+))                                            | EDV: 110 ± 32 (HE (-))<br>ESV: 56 ± 25 (HE (-))<br>EDV: 149 ± 40 (HE (+))<br>ESV: 93 ± 34 (HE (+))                                                                                | 49 ± 10 (HE (-))<br>39 ± 8 (HE (+))                                              |
| Wong,<br>2013       | 64  | 30g [21-40]                                                                                   | ESV: 63 [50-75]                                                                                                                                                                  | 58 [49-62]                                                                    | EDV: 152 [133-192]<br>ESV: 55 [39-84]                                                                                                                                             | 61 [56-67]                                                                       |
| Yoon,<br>2013       | 84  | 34.7% ± 13.6% (distal protection)<br>35.7% ± 14.6% (control)                                  | EDV: 127 ± 30 (distal protection)<br>ESV: 55 ± 25 (distal protection)<br>EDV: 133 ± 29 (control)<br>ESV: 59 ± 28 (control)                                                       | 57.7 ± 12.8 (distal protection)<br>57.2 ± 13.0 (control)                      | EDV: 140 ± 39 (distal protection)<br>ESV: 59 ± 32 (distal protection)<br>EDV: 133 ± 37 (control)<br>ESV: 54 ± 28 (control)                                                        | 59.5 ± 12.9 (distal protection)<br>60.7 ± 14.7 (control)                         |

BMC, bone marrow-derived cells; BM-MNC, bone marrow-derived mononuclear cells; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EPO, erythropoietin; ESV, end-systolic volume; ESVI, end-systolic volume index; G-CSF, granulocyte-colony-stimulating factor; HE, heterogeneous enhancement; IC, intracoronary; IL-8, interleukin-8; IV, intravenous; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVR, left ventricular remodeling; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; PGC-1  $\alpha$ , Peroxisome proliferator-activated receptor gamma coactivator 1  $\alpha$ ; STEMI, ST-elevation myocardial infarction. Values are expressed as mean  $\pm$  standard deviation or median [interquartile range].

**Supplementary Table S4.** Modified Newcastle-Ottawa risk of bias scores for the non-interventional studies included in this systematic review. See Supplementary Methods 2 for explanation.

| First author, year        | Representativeness | Sample size | Lost to follow-up | Definition of LVR | Descriptive statistics | Total score |
|---------------------------|--------------------|-------------|-------------------|-------------------|------------------------|-------------|
| Biesbroek, 2017           | 0                  | 0           | 1                 | 1                 | 1                      | 3           |
| Bulluck, 2016             | 0                  | 0           | 1                 | 1                 | 1                      | 3           |
| Caldentey, 2017           | 0                  | 1           | 1                 | 1                 | 1                      | 4           |
| Carberry, 2017            | 0                  | 1           | 1                 | 1                 | 1                      | 4           |
| Cha, 2019                 | 0                  | 0           | 0                 | 1                 | 1                      | 2           |
| Fabregat-Andrés, 2015     | 0                  | 0           | 0                 | 1                 | 1                      | 2           |
| Garcia, 2019              | 1                  | 1           | 0                 | 1                 | 1                      | 4           |
| Garg, 2017                | 0                  | 0           | 1                 | 1                 | 1                      | 3           |
| Gerbaud, 2014             | 0                  | 1           | 1                 | 1                 | 1                      | 4           |
| Gohbara, 2015             | 0                  | 0           | 0                 | 1                 | 1                      | 2           |
| Husser, 2013              | 0                  | 1           | 1                 | 1                 | 1                      | 4           |
| Huttin, 2017              | 0                  | 1           | 1                 | 0                 | 1                      | 3           |
| Mele, 2017                | 0                  | 0           | 0                 | 1                 | 1                      | 2           |
| O'Regan, 2012             | 0                  | 0           | 0                 | 1                 | 1                      | 2           |
| Pokorney, 2012            | 0                  | 0           | 0                 | 0                 | 1                      | 1           |
| Reindl, 2018              | 1                  | 1           | 1                 | 1                 | 1                      | 5           |
| Reinstadler, 2013         | 0                  | 0           | 1                 | 1                 | 1                      | 3           |
| Rodriguez-Palomares, 2019 | 0                  | 1           | 0                 | 1                 | 1                      | 3           |
| Shetye, 2017              | 0                  | 0           | 0                 | 1                 | 1                      | 2           |
| Sugano, 2017              | 0                  | 0           | 1                 | 1                 | 1                      | 3           |
| Symons, 2016              | 0                  | 1           | 1                 | 1                 | 1                      | 4           |
| Tanimoto, 2010            | 1                  | 1           | 1                 | 1                 | 0                      | 4           |
| Van Melle, 2010           | 0                  | 0           | 0                 | 1                 | 0                      | 1           |
| Watabe, 2016              | 1                  | 0           | 1                 | 1                 | 1                      | 4           |
| Wong, 2013                | 1                  | 0           | 1                 | 0                 | 1                      | 3           |

**Supplementary Table S5.** Assessment of risk of bias in the randomized controlled trials included in this review, using the Cochrane Collaboration's tool (Higgins et al. 2011).

|                                        | Achilli, 2014 | Eitel, 2011 | Grabmaier, 2017 | Hallen, 2010 | Janssens, 2018 | Mangion, 2016 | Najjar 2011 | Shetelig, 2018 | Sörensson, 2013 | Sürder, 2016 | Traverse, 2010 | Yoon, 2013 |
|----------------------------------------|---------------|-------------|-----------------|--------------|----------------|---------------|-------------|----------------|-----------------|--------------|----------------|------------|
| Random sequence generation             |               |             |                 |              |                |               |             |                |                 |              |                |            |
| Allocation concealment                 |               |             |                 |              |                |               |             |                |                 |              |                |            |
| Blinding of participants and personnel |               |             |                 |              |                |               |             |                |                 |              |                |            |
| Blinding of outcome assessment         |               |             |                 |              |                |               |             |                |                 |              |                |            |
| Incomplete outcome data                |               |             |                 |              |                |               |             |                |                 |              |                |            |
| Selective reporting                    |               |             |                 |              |                |               |             |                |                 |              |                |            |
| Other bias                             |               |             |                 |              |                |               |             |                |                 |              |                |            |

Key:

|  |                      |
|--|----------------------|
|  | low risk of bias     |
|  | high risk of bias    |
|  | unclear risk of bias |

**Supplementary Table 6.** Sensitivity analysis of the prevalence of left ventricular remodeling among patients with ST-elevation myocardial infarction. 95%-CI: 95% confidence interval.

Influential analysis (Random effects model)

|                                      | proportion | 95%-CI          | p-value | tau <sup>2</sup> | I <sup>2</sup> |
|--------------------------------------|------------|-----------------|---------|------------------|----------------|
| Omitting Fabregat-Andrés Ó 2015      | 0.2221     | [0.1884-0.2598] |         | 0.2259           | 81.6%          |
| Omitting Bulluck H 2016              | 0.2290     | [0.1938-0.2686] |         | 0.2419           | 82.6%          |
| Omitting Mele D 2017                 | 0.2277     | [0.1925-0.2672] |         | 0.2433           | 82.7%          |
| Omitting Biesbroek PS 2017           | 0.2294     | [0.1941-0.2689] |         | 0.2415           | 82.6%          |
| Omitting O'Regan DP 2012             | 0.2246     | [0.1899-0.2636] |         | 0.2394           | 82.4%          |
| Omitting Reinstadler SJ 2013         | 0.2316     | [0.1964-0.2709] |         | 0.2357           | 82.3%          |
| Omitting van Melle JP 2010           | 0.2298     | [0.1945-0.2694] |         | 0.2411           | 82.6%          |
| Omitting Garg P 2017                 | 0.2291     | [0.1938-0.2687] |         | 0.2425           | 82.6%          |
| Omitting Shetye AM 2017              | 0.2304     | [0.1950-0.2700] |         | 0.2402           | 82.5%          |
| Omitting Pokorney SD 2012            | 0.2299     | [0.1945-0.2696] |         | 0.2417           | 82.5%          |
| Omitting Sörensson P 2013            | 0.2319     | [0.1967-0.2714] |         | 0.2347           | 82.2%          |
| Omitting Sugano A 2017               | 0.2250     | [0.1900-0.2642] |         | 0.2422           | 82.4%          |
| Omitting Gohbara M 2015              | 0.2270     | [0.1916-0.2667] |         | 0.2459           | 82.7%          |
| Omitting Mangion K 2016              | 0.2312     | [0.1958-0.2707] |         | 0.2379           | 82.3%          |
| Omitting Cha MJ 2019                 | 0.2275     | [0.1920-0.2674] |         | 0.2471           | 82.7%          |
| Omitting Yoon CH 2013                | 0.2292     | [0.1936-0.2690] |         | 0.2447           | 82.6%          |
| Omitting Watabe H 2016               | 0.2250     | [0.1899-0.2645] |         | 0.2442           | 82.4%          |
| Omitting Reindl M 2018               | 0.2318     | [0.1964-0.2713] |         | 0.2357           | 82.1%          |
| Omitting Tanimoto T 2010             | 0.2292     | [0.1936-0.2692] |         | 0.2458           | 82.6%          |
| Omitting Eitel I 2011                | 0.2208     | [0.1886-0.2568] |         | 0.1992           | 79.0%          |
| Omitting Huttin O 2017               | 0.2255     | [0.1901-0.2653] |         | 0.2481           | 82.5%          |
| Omitting Gerbaud E 2014              | 0.2263     | [0.1907-0.2663] |         | 0.2505           | 82.6%          |
| Omitting Garcia G 2019               | 0.2311     | [0.1955-0.2710] |         | 0.2398           | 81.9%          |
| Omitting Caldentey G 2017            | 0.2337     | [0.1990-0.2724] |         | 0.2186           | 80.6%          |
| Omitting Husser O 2013               | 0.2220     | [0.1898-0.2578] |         | 0.1949           | 77.7%          |
| Omitting Carberry J 2017             | 0.2352     | [0.2013-0.2728] |         | 0.2011           | 79.1%          |
| Omitting Rodriguez-Palomares JF 2019 | 0.2257     | [0.1891-0.2669] |         | 0.2693           | 82.3%          |
| Omitting Symons R 2016               | 0.2291     | [0.1926-0.2703] |         | 0.2620           | 82.3%          |
| Pooled estimate                      | 0.2282     | [0.1938-0.2668] |         | 0.2377           | 82.0%          |

## REFERENCES

- Achilli F, Malafronte C, Maggiolini S, Lenatti L, Squadroni L, Gibelli G, Capogrossi MC, Dadone V, Gentile F, Bassetti B, Di Gennaro F, Camisasca P, Calchera I, Valagussa L, Colombo GI, Pompilio G; STEM-AMI trial Investigators. G-CSF treatment for STEMI: final 3-year follow-up of the randomised placebo-controlled STEM-AMI trial. *Heart* 2014;100:574-81. doi: 10.1136/heartjnl-2013-304955.
- Biesbroek PS, Amier RP, Teunissen PFA, Hofman MBM, Robbers LFHJ, van de Ven PM, Beek AM, van Rossum AC, van Royen N, Nijveldt R. Changes in remote myocardial tissue after acute myocardial infarction and its relation to cardiac remodeling: a CMR T1 mapping study. *PLoS One* 2017;12:e0180115. doi: 10.1371/journal.pone.0180115.
- Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuva AN, Treibel TA, Fontana M, Ramlall M, Hamarneh A, Sirker A, Herrey AS, Manisty C, Yellon DM, Kellman P, Moon JC, Hausenloy DJ. Residual myocardial iron following intramyocardial hemorrhage during the convalescent phase of reperfused ST-segment-elevation myocardial infarction and adverse left ventricular remodeling. *Circ Cardiovasc Imaging* 2016;9:e004940. doi:10.1161/CIRCIMAGING.116.004940.
- Caldentey G, García De Frutos P, Cristóbal H, Garabito M, Berruezo A, Bosch X, San Antonio R, Flores-Umanzor E, Perea RJ, De Caralt TM, Rodríguez J, Ortiz-Pérez JT. Serum levels of growth arrest-specific 6 protein and soluble AXL in patients with ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2017;2048872617740833. doi: 10.1177/2048872617740833.
- Carberry J, Carrick D, Haig C, Ahmed N, Mordi I, McEntegart M, Petrie MC, Eteiba H, Hood S, Watkins S, Lindsay M, Davie A, Mahrous A, Ford I, Sattar N, Welsh P, Radjenovic A, Oldroyd KG, Berry C. Persistence of infarct zone T2 hyperintensity at 6 months after acute ST-segment-elevation myocardial infarction: incidence, pathophysiology, and prognostic implications. *Circ Cardiovasc Imaging* 2017;10:e006586. doi: 10.1161/CIRCIMAGING.117.006586.
- Cha MJ, Lee JH, Jung HN, Kim Y, Choe YH, Kim SM. Cardiac magnetic resonance-tissue tracking for the early prediction of adverse left ventricular remodeling after ST-segment elevation myocardial infarction. *Int J Cardiovasc Imaging*. 2019. doi: 10.1007/s10554-019-01659-w.
- Eitel I, Friedenberger J, Fuernau G, Dumjahn A, Desch S, Schuler G, Thiele H. Intracoronary versus intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: 6-month effects on infarct size and left ventricular function. The randomised leipzig immediate percutaneous coronary intervention abciximab i.v. versus i.c. in ST-elevation myocardial infarction trial (LIPSIAbciximab-STEMI). *Clin Res Cardiol* 2011;100:425-32. doi: 10.1007/s00392-010-0260-5.
- Fabregat-Andrés Ó, Ridocci-Soriano F, Estornell-Erill J, Corbí-Pascual M, Valle-Muñoz A, Berenguer-Jofresa A, Barrabés JA, Mata M, Monsalve M. Blood PGC-1alpha concentration predicts myocardial salvage and ventricular remodeling after ST-segment elevation acute myocardial infarction. *Rev Esp Cardiol (Engl Ed)* 2015;68:408-16. doi: 10.1016/j.rec.2014.05.020.
- Garcia G, Chao de la Barca JM, Mirebeau-Prunier D, Reynier P, Furber A, Prunier F, Bière L. Metabolomic Approach in STEMI-Patients Undergoing Left Ventricular Remodeling. *Int J Mol Sci*. 2019;20. pii: E289. doi: 10.3390/ijms20020289.
- Garg P, Broadbent DA, Swoboda PP, Foley JRJ, Fent GJ, Musa TA, Ripley DP, Erhayiem B, Dobson LE, McDiarmid AK, Haaf P, Kidambi A, Crandon S, Chew PG, van der Geest RJ, Greenwood JP, Plein S. Extra-cellular expansion in the normal, non-infarcted myocardium

- is associated with worsening of regional myocardial function after acute myocardial infarction. *J Cardiovasc Magn Reson* 2017;19:73. doi: 10.1186/s12968-017-0384-0.
- Gerbaud E, Montaudon M, Chasseraud W, Gilbert S, Cochet H, Pucheu Y, Horovitz A, Bonnet J, Douard H, Coste P. Effect of ivabradine on left ventricular remodelling after reperfused myocardial infarction: a pilot study. *Arch Cardiovasc Dis* 2014;107:33-41. doi: 10.1016/j.acvd.2013.12.001.
- Gohbara M, Iwahashi N, Kataoka S, Hayakawa Y, Sakamaki K, Akiyama E, Maejima N, Tsukahara K, Hibi K, Kosuge M, Ebina T, Umemura S, Kimura K. Glycemic variability determined by continuous glucose monitoring system predicts left ventricular remodeling in patients with a first ST-segment elevation myocardial infarction. *Circ J* 2015;79:1092-9. doi: 10.1253/circj.CJ-14-1226.
- Grabmaier U, Clauss S, Gross L, Klier I, Franz WM, Steinbeck G, Wakili R, Theiss HD, Brenner C. Diagnostic and prognostic value of miR-1 and miR-29b on adverse ventricular remodeling after acute myocardial infarction - The SITAGRAMI-miR analysis. *Int J Cardiol* 2017;244:30-6. doi: 10.1016/j.ijcard.2017.06.054.
- Hallén J, Jensen JK, Fagerland MW, Jaffe AS, Atar D. Cardiac troponin I for the prediction of functional recovery and left ventricular remodelling following primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Heart* 2010;96:1892-7. doi: 10.1136/hrt.2009.190819.
- Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Husser O, Monmeneu JV, Sanchis J, Nunez J, Lopez-Lereu MP, Bonanad C, Chaustre F, Gomez C, Bosch MJ, Hinarejos R, Chorro FJ, Riegger GA, Llacer A, Bodi V. Cardiovascular magnetic resonance-derived intramyocardial hemorrhage after STEMI: influence on long-term prognosis, adverse left ventricular remodeling and relationship with microvascular obstruction. *Int J Cardiol* 2013;167:2047-54. doi: 10.1016/j.ijcard.2012.05.055.
- Huttin O, Mandry D, Eschalier R, Zhang L, Micard E, Odille F, Beaumont M, Fay R, Felblinger J, Camenzind E, Zannad F, Girerd N, Marie PY. Cardiac remodeling following reperfused acute myocardial infarction is linked to the concomitant evolution of vascular function as assessed by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2017;19:2. doi: 10.1186/s12968-016-0314-6.
- Janssens SP, Bogaert J, Zalewski J, Toth A, Adriaenssens T, Belmans A, Bennett J, Claus P, Desmet W, Dubois C, Goetschalckx K, Sinnaeve P, Vandenberghe K, Vermeersch P, Lux A, Szellid Z, Durak M, Lech P, Zmudka K, Pokreisz P, Vranckx P, Merkely B, Bloch KD, Van de Werf F; NOMI investigators. Nitric oxide for inhalation in ST-elevation myocardial infarction (NOMI): a multicentre, double-blind, randomized controlled trial. *Eur Heart J* 2018;39(29):2717-25. *Eur Heart J*. 2018 Aug 1;39:2717-2725.
- Mangion K, Carrick D, Hennigan BW, Payne AR, McClure J, Mason M, Das R, Wilson R, Edwards RJ, Petrie MC, McEntegart M, Eteiba H, Oldroyd KG, Berry C. Infarct size and left ventricular remodelling after preventive percutaneous coronary intervention. *Heart* 2016;102:1980-7. doi: 10.1136/heartjnl-2015-308660.
- Mele D, Nardoza M, Chiodi E. Early speckle-tracking echocardiography predicts left ventricle remodeling after acute ST-segment elevation myocardial infarction. *J Cardiovasc Echogr* 2017;27:93-8. doi: 10.4103/jcecho.jcecho\_2\_17.
- Najjar SS, Rao SV, Melloni C, Raman SV, Povsic TJ, Melton L, Barsness GW, Prather K, Heitner JF, Kilari R, Gruberg L, Hasselblad V, Greenbaum AB, Patel M, Kim RJ, Talan M, Ferrucci L, Longo DL, Lakatta EG, Harrington RA; REVEAL Investigators. Intravenous erythropoietin

- in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. *JAMA* 2011;305:1863-72. doi: 10.1001/jama.2011.592.
- O'Regan DP, Shi W, Ariff B, Baksi AJ, Durighel G, Rueckert D, Cook SA. Remodeling after acute myocardial infarction: mapping ventricular dilatation using three dimensional CMR image registration. *J Cardiovasc Magn Reson* 2012;14:41. doi: 10.1186/1532-429X-14-41.
- Pokorney SD, Rodriguez JF, Ortiz JT, Lee DC, Bonow RO, Wu E. Infarct healing is a dynamic process following acute myocardial infarction. *J Cardiovasc Magn Reson* 2012;14:62. doi: 10.1186/1532-429X-14-62.
- Reindl M, Feistritzer HJ, Reinstadler SJ, Mueller L, Tiller C, Brenner C, Mayr A, Henninger B, Mair J, Klug G, Metzler B. Thyroid-stimulating hormone and adverse left ventricular remodeling following ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2018;2048872618770600. doi: 10.1177/2048872618770600.
- Reinstadler SJ, Klug G, Feistritzer HJ, Mayr A, Harrasser B, Mair J, Bader K, Streil K, Hammerer-Lercher A, Esterhammer R, Metzler B. Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. *Heart* 2013;99:1525-9. doi: 10.1136/heartjnl-2013-303975.
- Rodriguez-Palomares JF, Gavara J, Ferreira-González I, Valente F, Rios C, Rodríguez-García J, Bonanad C, García Del Blanco B, Miñana G, Mutuberria M, Nuñez J, Barrabés J, Evangelista A, Bodí V, García-Dorado D. Prognostic Value of Initial Left Ventricular Remodeling in Patients With Reperfused STEMI. *JACC Cardiovasc Imaging*. 2019; doi: 10.1016/j.jcmg.2019.02.025.
- Shetelig C, Limalanathan S, Hoffmann P, Seljeflot I, Gran JM, Eritsland J, Andersen GØ. Association of IL-8 With Infarct Size and Clinical Outcomes in Patients With STEMI. *J Am Coll Cardiol* 2018;72:187-98. doi: 10.1016/j.jacc.2018.04.053.
- Shetye AM, Nazir SA, Razvi NA, Price N, Khan JN, Lai FY, Squire IB, McCann GP, Arnold JR. Comparison of global myocardial strain assessed by cardiovascular magnetic resonance tagging and feature tracking to infarct size at predicting remodelling following STEMI. *BMC Cardiovasc Disord* 2017;17:7. doi: 10.1186/s12872-016-0461-6.
- Sörensson P, Rydén L, Saleh N, Tornvall P, Arheden H, Pernow J. Long-term impact of postconditioning on infarct size and left ventricular ejection fraction in patients with ST-elevation myocardial infarction. *BMC Cardiovasc Disord* 2013;13:22. doi: 10.1186/1471-2261-13-22.
- Sugano A, Seo Y, Ishizu T, Watabe H, Yamamoto M, Machino-Ohtsuka T, Takaiwa Y, Kakefuda Y, Aihara H, Fumikura Y, Nishina H, Noguchi Y, Aonuma K. Value of 3-Dimensional speckle tracking echocardiography in the prediction of microvascular obstruction and left ventricular remodeling in patients with ST-elevation myocardial infarction. *Circ J* 2017;81:353-60. doi: 10.1253/circj.CJ-16-0944.
- Sürder D, Manka R, Moccetti T, Lo Cicero V, Emmert MY, Klersy C, Soncin S, Turchetto L, Radrizzani M, Zuber M, Windecker S, Moschovitis A, Bühler I, Kozerke S, Erne P, Lüscher TF, Corti R. Effect of Bone Marrow-Derived Mononuclear Cell Treatment, Early or Late After Acute Myocardial Infarction: Twelve Months CMR and Long-Term Clinical Results. *Circ Res* 2016;119:481-90. doi: 10.1161/CIRCRESAHA.116.308639.
- Symons R, Masci PG, Francone M, Claus P, Barison A, Carbone I, Agati L, Galea N, Janssens S, Bogaert J. Impact of active smoking on myocardial infarction severity in reperfused ST-segment elevation myocardial infarction patients: the smoker's paradox revisited. *Eur Heart J* 2016;37:2756-64. doi: 10.1093/eurheartj/ehv738.
- Tanimoto T, Imanishi T, Kitabata H, Nakamura N, Kimura K, Yamano T, Ishibashi K, Komukai K, Ino Y, Takarada S, Kubo T, Hirata K, Mizukoshi M, Tanaka A, Akasaka T. Prevalence and clinical significance of papillary muscle infarction detected by late gadolinium-enhanced

- magnetic resonance imaging in patients with ST-segment elevation myocardial infarction. *Circulation* 2010;122:2281-7. doi: 0.1161/CIRCULATIONAHA.109.935338.
- Traverse JH, McKenna DH, Harvey K, Jorgensen BC, Olson RE, Bostrom N, Kadidlo D, Lesser JR, Jagadeesan V, Garberich R, Henry TD. Results of a phase 1, randomized, double-blind, placebo-controlled trial of bone marrow mononuclear stem cell administration in patients following ST-elevation myocardial infarction. *Am Heart J* 2010;160:428-34. doi: 10.1016/j.ahj.2010.06.009.
- van Melle JP, van der Vleuten PA, Hummel YM, Nijveldt R, Tio RA, Voors AA, Zijlstra F. Predictive value of tissue doppler imaging for left ventricular ejection fraction, remodelling, and infarct size after percutaneous coronary intervention for acute myocardial infarction. *Eur J Echocardiogr* 2010;11:596-601. doi: 10.1093/ejehocardiography/jeq023.
- Watabe H, Sato A, Nishina H, Hoshi T, Sugano A, Kakefuda Y, Takaiwa Y, Aihara H, Fumikura Y, Noguchi Y, Aonuma K. Enhancement patterns detected by multidetector computed tomography are associated with microvascular obstruction and left ventricular remodelling in patients with acute myocardial infarction. *Eur Heart J* 2016;37:684-92. doi: 10.1093/eurheartj/ehv467.
- Wong DT, Leung MC, Das R, Liew GY, Teo KS, Chew DP, Meredith IT, Worthley MI, Worthley SG. Intracoronary ECG during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction predicts microvascular obstruction and infarct size. *Int J Cardiol* 2013;165(1):61-6. doi: 10.1016/j.ijcard.2011.07.078.
- Yoon CH, Chung WY, Suh JW, Cho YS, Youn TJ, Chun EJ, Choi SI, Chae IH, Choi DJ. Distal protection device aggravated microvascular obstruction evaluated by cardiac MR after primary percutaneous intervention for ST-elevation myocardial infarction. *Int J Cardiol* 2013;167:2002-7. doi: 10.1016/j.ijcard.2012.05.029.

## Definition of left ventricular remodeling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies

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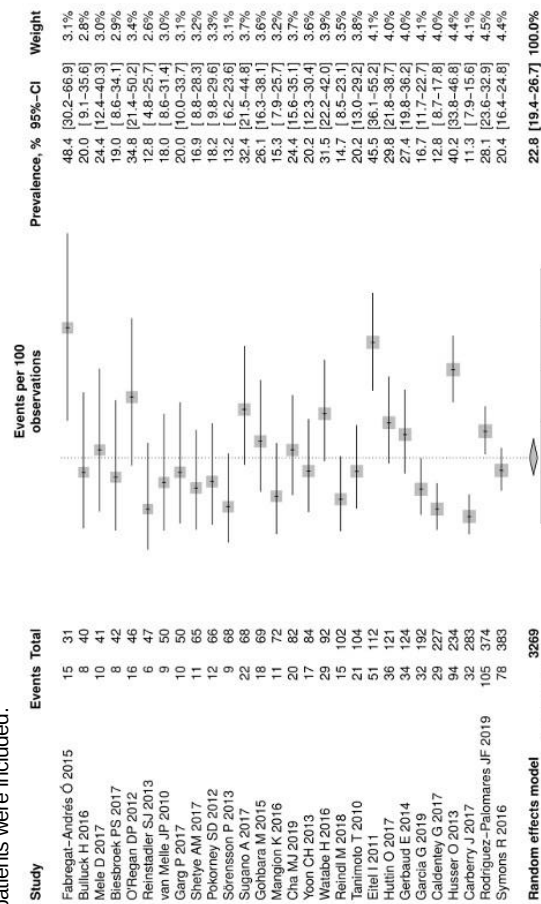


**Purpose.** An increase in left ventricular volumes between baseline and follow-up imaging is the main criteria for the quantification of left ventricular remodeling (LVR) after ST-elevation myocardial infarction, but without consensual definition. We aimed to review the criterion used for the definition of left ventricular remodeling based on cardiac magnetic resonance imaging in studies including patients with ST-elevation myocardial infarction.

**Methods.** A systematic literature search was conducted using MEDLINE and the Cochrane Library from January 2010 to August 2019. Thirty-seven studies involving a total of 4209 patients were included.

**Results.** The median age of the patients was 59 years, 82 % were male, and 93 % underwent primary percutaneous coronary intervention. The median follow-up duration was 6 months (range, 3–12), and the second cardiac magnetic resonance session was performed at 6 months in 14 (38%) studies. Among these studies, 30 (81%) used a cut-off value for defining LVR, with a pooled LVR prevalence estimate of 22.8%, 95%-CI[19.4%-26.7%], and a major between-study heterogeneity ( $I^2=82\%$ ). The seven remaining studies (19%) defined LVR as a continuous variable. A 20% increase in end-diastolic volumes or a 15% increase in end-systolic volumes between a baseline and a follow-up cardiac magnetic resonance imaging were the two most common criterion (13 [35%] and 9 [24%] studies, respectively). Seven studies used both end-diastolic and end-systolic left ventricular volumes.

**Conclusions.** The definition of LVR using cardiac magnetic resonance following ST-elevation myocardial infarction is highly variable, among studies including highly selected patients. The most frequent LVR criterion were a 20% increase in end-diastolic volumes or a 15% increase in end-systolic volumes. A composite cut-off value of a 12% to 15% increase in end-systolic volume and a 12% to 20% increase in end-diastolic volume using a follow-up cardiac magnetic resonance imaging 1 to 3 months after myocardial infarction might be proposed as a consensual cut-off for defining LVR for future large-sized, prospective studies with serial cardiac magnetic resonance imaging and long-term follow-up in unselected patients.



Meta-analysis of the prevalence of left ventricular remodeling among patients presenting with STEMI using CMR imaging. The square area is proportional to the inverse variance of the estimate

## **Étude REMOD-TEP, poster présenté aux JESFC 2016**

Poster présenté aux JESFC 2016, dans les suites de l'obtention en décembre 2015 de la bourse SFC "Les syndromes coronariens aigus", de 20000 €.

# Relationship between left ventricular remodeling, coronary endothelial function and myocardial fibrosis using positron emission tomography in patients with ST-elevation myocardial infarction (REMOT-TEP)

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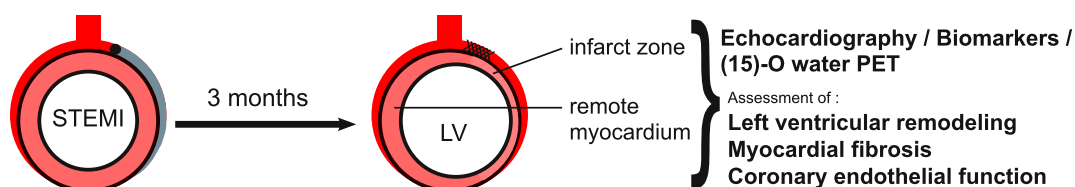
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**Background.** Left ventricular remodeling is a common complication in patients with ST-elevation myocardial infarction (STEMI) and may lead to heart failure. Hemodynamic, metabolic and inflammatory mechanisms are involved in this pathophysiological process. Recent data demonstrated that remote, noninfarct-related region of the myocardium is also implicated. There is no data about the assessment of coronary endothelial function or myocardial fibrosis in the remote zone in patients with STEMI. The correlation between these parameters and left ventricular remodeling is not known.



**Primary objective.** Assessment of coronary endothelial function and myocardial fibrosis 3 months after onset of STEMI (infarct-related and remote myocardium).

**Secondary objectives.** Correlation between global and regional coronary endothelial function, myocardial fibrosis and echocardiographic parameters of left ventricular remodeling (3 months).

**Methods.** A total of 30 patients with STEMI successfully treated with primary coronary intervention (TIMI 3) and single-vessel coronary artery disease will be included. Transthoracic echocardiography and measurements of biomarkers of endothelial function, fibrosis and inflammation (MMP-2, hsCRP, fibrinogen, IL-1, and TNF-alpha) will be performed during the initial hospitalization and after 3 months. Coronary endothelial function will be assessed using (15)-O water positron emission tomography (PET) at rest and after cold pressor test at 3 months. Fibrosis will be quantified using the amount of perfusable tissue fraction assessed by (15)-O water PET. These quantitative parameters will be compared between remote and infarct myocardium and correlated with left ventricular remodeling and biomarkers.

**Conclusion.** This study will provide valuable information on the mechanisms involved in left ventricular remodeling following STEMI, with a special focus on the role of remote myocardium.

## **Relation entre le strain atrial gauche et le remodelage ventriculaire gauche**

Cette annexe concerne le manuscrit suivant: **Legallois D**, Hodzic A, Milliez P, Manrique A, Saloux E, Beygui F. Left atrial strain quantified after myocardial infarction is associated with ventricular remodeling. Soumis à American Journal of Cardiology.

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## Left atrial strain is associated with left ventricular remodeling in patients with ST-elevation myocardial infarction

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**Purpose.** Left ventricular remodeling (LVR) is associated with outcomes in patients with ST-elevation myocardial infarction (STEMI). Left atrial (LA) volume has been described as a predictor of outcomes in the latter population. We investigated the association between LA mechanical function using speckle tracking imaging and LVR at follow-up after STEMI.

**Methods.** Baseline and 6-month 3D transthoracic echocardiograms were performed in 121 STEMI patients. LA global longitudinal strain was reported for the reservoir (LASr), conduit (LAScd), and contraction (LASct) phases.

**Results.** Mean age was 58.3±12.5 years and 98 (81%) were men. Baseline left ventricular ejection fraction (LVEF) was 46.8% [41.0, 52.9] and improved to 52.1% [45.8, 57.0] at follow-up, ( $p<0.001$ ). A lower LASct was associated with a dilation of left ventricle at follow-up (%end-diastolic volume increase: -1.9% [-11.0, 15.2] in the two higher LASct tertiles group vs. 19.2% [5.0, 34.3] in the lower LASct tertile group,  $p=0.001$ ). A higher %end-systolic volume increase at follow-up was associated with lower LASct: 12.6% [-16.2, 39.8] in the lower LASct group vs. -6.8% [-23.6, 14.4] in the two higher LASct tertiles group ( $p=0.004$ ). Regarding LVEF, a low LVEF at follow-up was associated with the worst tertile of all LA strains.

**Conclusions.** The three components of baseline LA strain were associated with LVEF at follow-up in patients with STEMI. Some of these components were also significantly associated with lower LVEF at baseline or predictive of a significant increase in left ventricular volumes during follow-up, indicating LVR.

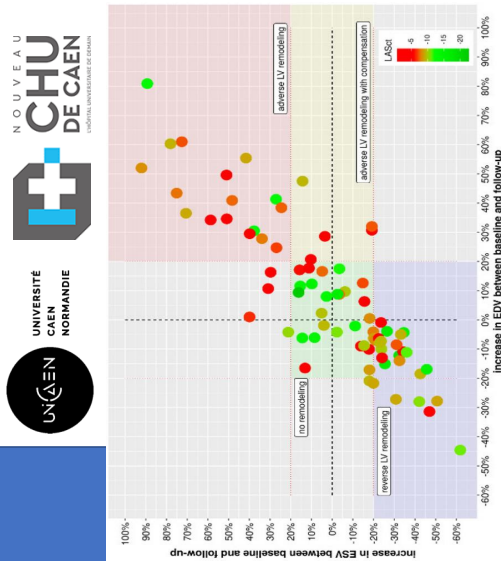


Figure. Relationship between LASct and remodeling pattern after STEMI

|                                       | Overall<br>(n=121)  | Lowest LASr tertile<br>(abs. values)<br>(n=40) | Other tertiles<br>(abs. values)<br>(n=81) | p.value | Lowest LAScd tertile<br>(abs. values)<br>(n=40) | Other tertiles<br>(abs. values)<br>(n=81) | p.value | Lowest LASct tertile<br>(abs. values)<br>(n=40) | Other tertiles<br>(abs. values)<br>(n=81) | p.value |
|---------------------------------------|---------------------|------------------------------------------------|-------------------------------------------|---------|-------------------------------------------------|-------------------------------------------|---------|-------------------------------------------------|-------------------------------------------|---------|
| <b>Echocardiography, at baseline</b>  |                     |                                                |                                           |         |                                                 |                                           |         |                                                 |                                           |         |
| EDV, mL/m2                            | 56 [48, 67]         | 60 [52, 66]                                    | 55 [47, 68]                               | 0.38    | 60 [53, 67]                                     | 55 [47, 66]                               | 0.32    | 54 [46, 65]                                     | 58 [49, 67]                               | 0.25    |
| ESV, mL/m2                            | 30 [24, 36]         | 32 [27, 38]                                    | 28 [23, 35]                               | 0.18    | 33 [27, 39]                                     | 29 [24, 35]                               | 0.12    | 30 [25, 38]                                     | 31 [24, 36]                               | 0.91    |
| LVEF, %                               | 46.8 [41.0, 52.9]   | 44.8 [40.0, 49.3]                              | 48.4 [42.3, 54.0]                         | 0.042   | 44.9 [39.1, 49.3]                               | 48.2 [42.5, 54.0]                         | 0.026   | 44.9 [39.8, 50.3]                               | 48.4 [42.4, 53.3]                         | 0.067   |
| <b>Echocardiography, at follow-up</b> |                     |                                                |                                           |         |                                                 |                                           |         |                                                 |                                           |         |
| EDV, mL/m2                            | 59 [49, 72]**       | 60 [49, 78]*                                   | 59 [49, 70]*                              | 0.67    | 62 [53, 76]**                                   | 57 [48, 70]*                              | 0.20    | 64 [52, 80]**                                   | 58 [48, 70]                               | 0.20    |
| % Increase in EDV, %                  | 7.7 [-8.4, 24.9]    | 9.2 [-7.7, 19.6]                               | 3.3 [-8.3, 27.5]                          | 0.99    | 9.3 [-6.2, 17.6]                                | 2.8 [-10.1, 27.5]                         | 0.48    | 19.2 [5.0, 34.3]                                | -1.9 [-11.0, 15.2]                        | <0.001  |
| ESV, mL/m2                            | 27 [21, 40]         | 30 [22, 45]                                    | 27 [20, 36]                               | 0.13    | 31 [25, 43]                                     | 26 [20, 37]                               | 0.047   | 31 [22, 46]*                                    | 27 [20, 37]                               | 0.06    |
| % Increase in ESV, %                  | -2.6 [-21.0, 21.3]  | 2.2 [-20.6, 31.7]                              | -3.5 [-20.9, 21.2]                        | 0.42    | 2.2 [-20.6, 23.5]                               | -3.7 [-20.9, 21.6]                        | 0.52    | 12.6 [-16.2, 39.8]                              | -6.8 [-23.6, 14.4]                        | 0.004   |
| LVEF, %                               | 52.1 [45.8, 57.0]** | 48.2 [41.9, 54.7]                              | 54.0 [48.1, 59.5]**                       | 0.002   | 49.2 [42.9, 54.4]*                              | 54.4 [48.1, 59.4]**                       | 0.01    | 48.2 [39.9, 54.9]                               | 53.2 [47.4, 59.2]**                       | 0.01    |

Table. Echocardiographic data according to left atrial strain status. \* $p<0.05$ , \*\* $p<0.01$  and \*\*\* $p<0.001$  vs. baseline.

## **Biomarqueurs et remodelage ventriculaire gauche : revue de la littérature**

Ces annexes concernent le manuscrit suivant: **Legallois D**, Hodzic A, Allouche S, Milliez P, Beygui F. The relationship between circulating biomarkers and left ventricular remodeling after my-ocardial infarction: an updated review. Soumis à Disease Markers.

## **The relationship between circulating biomarkers and left ventricular remodeling after myocardial infarction: an updated review**

Heart Failure Reviews - Online resource

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**SUPPLEMENTAL MATERIAL**

**Supplementary Table S1.** Association between infarct size-related biomarkers levels and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction; CMR, cardiac magnetic resonance; LVEDD, left ventricular end-diastolic diameter; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV(i), (indexed) left ventricular end-systolic volume ; IQR, interquartile range; LVR, left ventricular remodeling; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; SPECT, single photon emission computed tomography; STEMI, ST-elevation myocardial infarction; TTE, transthoracic echocardiography.

**Supplementary Table S2.** Association between natriuretic peptides, biomarkers of inflammation or involved in the turnover of matrix and collagen synthesis levels and LVR at follow-up in STEMI patients. Only data not available in the main manuscript are provided in this supplementary table. AMI, acute myocardial infarction; ANP, atrial natriuretic peptide; CMR, cardiac magnetic resonance; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV, left ventricular end-systolic volume ; LVR, left ventricular remodeling; MMP, matrix metalloproteinase; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; STEMI, ST-elevation myocardial infarction; TIMP, tissue inhibitor of metalloproteinase ; TNF, tumor necrosis factor; TTE, transthoracic echocardiography.

**Supplementary Table S3.** Association between routine biomarkers levels and LVR at follow-up in STEMI patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMR, cardiac magnetic resonance; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV, left ventricular end-systolic volume ; HbA1c, glycated hemoglobin; IQR, interquartile range; LVR, left ventricular remodeling; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiography.

**Supplementary Table S4.** Association between lipid profile and LVR at follow-up in STEMI patients. CMR, cardiac magnetic resonance; LVEDV(i), (indexed) left ventricular end-diastolic

volume ; LVESV, left ventricular end-systolic volume ; LVR, left ventricular remodeling; PCI, percutaneous coronary intervention; TTE, transthoracic echocardiography.

**Supplementary Table S5.** Association between remaining biomarkers levels, not described in other tables, and LVR in STEMI patients. ACE-2, angiotensin-converting enzyme 2; ADAMTS-7, A disintegrin and metalloproteinase with thrombospondin motifs 7; AMI, acute myocardial infarction; CMR, cardiac magnetic resonance; FGF, Fibroblast growth factor; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV(i), (indexed) left ventricular end-systolic volume ; LVR, left ventricular remodeling; MBL, Mannose-binding lectin; miR, micro RNA; PCI, percutaneous coronary intervention; PGC-1 $\alpha$ , Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SPECT, single photon emission computed tomography; STEMI, ST-elevation myocardial infarction; TTE, transthoracic echocardiography.

Table 1

| Table 1         | sample size                                      | design          | biomarker assessment                                                                                   | follow-up imaging                                                                   | definition of LVR                           | LVR                       | correlation            | reference                |
|-----------------|--------------------------------------------------|-----------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------|---------------------------|------------------------|--------------------------|
| Troponin I      | 62                                               | Prospective     | within 24 hours                                                                                        | TTE, 1 month                                                                        | ≥20% increase in LVEDV                      | 16 (26%)                  | none                   | Abdel Hamid 2016         |
|                 | 227                                              | Prospective     | every 6 hours during the first 12 hours and every 12 hours thereafter before discharge (average day 4) | CMR, 6 months                                                                       | ≥20% increase in LVEDV                      | 29 (16%)                  | none                   | Caldentey 2019           |
|                 | 230                                              | Prospective     |                                                                                                        | TTE, 6 months                                                                       | increase in LVEDV                           | 146 (50%)                 | none                   | Devaux 2012              |
|                 | 60 (derivation cohort)<br>30 (validation cohort) | Prospective     | day 3-4 (before discharge)                                                                             | TTE, 176 days (derivation cohort, n=60)<br>CMR, 12 months (validation cohort, n=30) | increase in LVEDV                           | 30 (50%)                  | none                   | Devaux 2013              |
| Peak troponin I | 92                                               | Prospective     | baseline                                                                                               | TTE, 6 months                                                                       | ≥15% increase in LVESV                      | 26 (28.2%)                | none                   | Di Tano 2017             |
|                 | 226 (Q-wave MI)                                  | Prospective     | at discharge (day 3 to day 7)                                                                          | TTE, 12 months                                                                      | >20% increase in LVEDV                      | 87 (38%)                  | positive               | Ferlin 2010              |
|                 | 132                                              | RCT substudy    | 24 hours, 48 hours                                                                                     | CMR, 4 months                                                                       | unavailable                                 | NA                        | positive               | Hallen 2010              |
|                 | 198                                              | Not available   | day 5                                                                                                  | TTE, 12 months                                                                      | ≥20% increase in LVEDV                      | 56 (28.3%)                | none                   | Liu 2015                 |
|                 | 48                                               | Prospective     | day 2, day 7                                                                                           | CMR, 1 month and 3 months                                                           | none                                        | NA                        | positive (day 2)       | Mathur 2013              |
|                 | 141                                              | Not available   | unavailable                                                                                            | TTE, 4 months                                                                       | ≥20% increase in LVEDV                      | 48 (34.8%)                | none                   | Zaladunyte-Peksiene 2014 |
| Peak troponin I | 75                                               | Prospective     | every 6 h after admission until peak values                                                            | TTE, 6 months                                                                       | ≥15% increase in LVEDV                      | 22 (29.3%)                | positive               | Karuzas 2019             |
|                 | 74                                               | Not available   | baseline                                                                                               | TTE, 3 months                                                                       | decrease in LVESV                           | NA                        | positive               | Acar 2016                |
|                 | 109                                              | Retrospective   | repeated measurements within the first 96 hours                                                        | TTE, 17 months                                                                      | ≥20% increase in LVEDV                      | 30 (28%)                  | positive               | Buono 2011               |
|                 | 131                                              | Not available   | every four hours after hospital admission for three days                                               | TTE, 6 months                                                                       | >20% increase in LVEDV                      | 42 (32%)                  | positive, multivariate | Choi 2013                |
|                 | 161 (AMI)                                        | Prospective     | at admission                                                                                           | TTE, 12 months                                                                      | >20% increase in LVEDV                      | 24 (14.9%)                | none                   | Dominguez-Rodriguez 2012 |
|                 | 97                                               | Prospective     | at admission                                                                                           | TTE, 12 months                                                                      | >20% increase in LVEDV                      | 21 (21.6%)                | none                   | Dominguez-Rodriguez 2011 |
|                 | 80                                               | Prospective     | at admission                                                                                           | TTE, 6 months                                                                       | ≥20% increase in LVEDV                      | 28 (36.3%)                | positive, multivariate | Ekel 2012                |
|                 | 58                                               | Prospective     | unavailable                                                                                            | CMR, 4 and 12 months                                                                | unavailable                                 | 18 (31%),<br>at 12 months | positive               | Ganiame 2011             |
|                 | 78                                               | Prospective     | within the first 24 to 96 hours after the onset of symptoms                                            | TTE and CMR, 6 months                                                               | >20% increase in LVEDV                      | 26 (31.7%)                | none                   | Garcia-Alvarez 2009      |
|                 | 97 (61 % STEMI)                                  | Prospective     | at first 3 days                                                                                        | TTE, 6 months                                                                       | >20% increase in LVEDV                      | 24 (32.9%)                | none                   | Hsu 2017                 |
| Troponin T      | 35                                               | prospective     | at admission                                                                                           | TTE, 2 months, 12 months                                                            | ≥20% increase in LVEDV (2 months)           | 14 (40%)                  | none                   | Khurelsukh 2016          |
|                 | 97                                               | Prospective     | unavailable                                                                                            | TTE, 6 months                                                                       | ≥20% increase in LVEDV                      | 38 (39.2%)                | positive, multivariate | Lacalzada 2015           |
|                 | 208                                              | Not available   | unavailable                                                                                            | TTE, 6 months                                                                       | >20% increase in LVEDV                      | 53 (25.5%)                | none                   | Na 2016                  |
|                 | 46                                               | Not available   | unavailable                                                                                            | CMR, 12 months                                                                      | ≥20% increase in LVEDV                      | 16 (35%)                  | none                   | O'Regan 2012             |
|                 | 88                                               | Prospective     | every 6 hours during the first 12 hours and every 12 hours thereafter, during 48 hours                 | CMR, 6.4 months                                                                     | ≥20% increase in LVEDV                      | 15 (16.9%)                | none                   | Ortiz-Perez 2013         |
|                 | 75                                               | Not available   | unavailable                                                                                            | TTE, 6 months                                                                       | ≥10% decrease in LVESV (reverse remodeling) | 25 (33.3%)                | positive               | Spinelli 2013            |
|                 | 198                                              | Prospective     | unavailable                                                                                            | TTE, 6 months                                                                       | >20% increase in LVEDV                      | 55 (27.8%)                | none                   | Swatkiewicz 2012         |
|                 | 383                                              | Prospective     | unavailable                                                                                            | CMR, 4 months                                                                       | >20% increase in LVEDV                      | unavailable               | positive               | Symons 2016              |
|                 | 110                                              | Prospective     | unavailable                                                                                            | TTE, 3 months                                                                       | ≥20% increase in LVEDV                      | 26 (23.6%)                | positive               | Xu 2017                  |
|                 | 87                                               | Prospective     | on admission and every 12 hours for at least 72 hours after PCI                                        | TTE, 6 months                                                                       | ≥15% increase in LVESV                      | 44 (50.6%)                | positive               | Spinelli 2018            |
| hs Troponin I   | 104                                              | Prospective     | every 4 hours until the values started to decrease                                                     | TTE, 6 months                                                                       | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%),<br>reverse    | none                   | Wu 2018                  |
|                 | 82                                               | Retrospective   | unavailable                                                                                            | CMR, 7 months                                                                       | ≥20% increase in LVEDV                      | 20 (24.4%)                | positive               | Cha 2019                 |
|                 | 64                                               | Matched cohorts | 48h [IQR 24-72]                                                                                        | CMR, 3 months, 12 months                                                            | >10% increase in LVESV                      | NA                        | none                   | Garcia 2019              |
|                 | 359 (AMI)                                        | Not available   | at admission                                                                                           | TTE, 6 months                                                                       | >10% increase in LVEDV                      | 116 (32.3%)               | positive               | Lv 2014                  |
|                 | 42                                               | Not available   | prior to PCI, day 2, week 1                                                                            | CMR, 2 months and 12 months                                                         | none                                        | NA                        | variable               | Manhenke 2014            |
|                 | 57                                               | Not available   | during PCI                                                                                             | TTE, 6 months                                                                       | ≥20% increase in LVESV                      | 22 (38.6%)                | none                   | Andrejic 2019            |
|                 | 39                                               | Prospective     | during PCI, 3 hours, 6 hours, 12 hours and/or 24 hours                                                 | TTE, 6 months                                                                       | ≥20% increase in LVEDV With LVESV<50 %      | 14 (35.9%)                | none                   | Galeano-Otero 2020       |
|                 | 213                                              | Retrospective   | baseline                                                                                               | TTE, 6 months                                                                       | ≥15% increase in LVESV                      | 44 (21%)                  | positive               | Alate 2014               |
|                 | 39                                               | RCT             | unavailable                                                                                            | TTE, 3 months                                                                       | ≥20% increase in LVEDV                      | 13 (33.3%)                | none                   | Ezbieciak 2013           |
|                 | 89                                               | Prospective     | serially                                                                                               | CMR, 4 months                                                                       | ≥20% increase in LVEDV                      | 14 (15.7%)                | positive, multivariate | Feistritz 2015           |
| Peak troponin T | 159                                              | Prospective     | unavailable                                                                                            | TTE, 6 months                                                                       | ≥20% increase in LVEDV                      | 31 (19.5%)                | positive               | Haldon 2010              |
|                 | 964                                              | Prospective     | unavailable                                                                                            | TTE, 6 months                                                                       | ≥20% increase in LVEDV                      | 296 (30.7%)               | positive               | Joyce 2013               |

Page 1

Table 1

|                                 |      |                 |                                                                                |                                         |                                             |             |                               |                    |
|---------------------------------|------|-----------------|--------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------|-------------|-------------------------------|--------------------|
|                                 | 35   | prospective     | at admission                                                                   | TTE, 2 months, 12 months                | ≥20% increase in LVEDV (CMR)                | 14 (40%)    | positive                      | Khursaihi 2016     |
|                                 | 112  | Not available   | unavailable                                                                    | TTE, 6 months                           | ≥15% increase in LVESV                      | 19 (17.0%)  | positive                      | Nucifora 2010      |
|                                 | 47   | Prospective     | before PCI, every 6 hours during 24 hours then daily until discharge           | CMR, 4 months                           | ≥20% increase in LVEDV                      | 6 (12.8%)   | positive                      | Reinstadler 2013   |
|                                 | 111  | Prospective     | baseline, 6 hours, 24 hours                                                    | TTE, 6 months                           | ≥20% increase in LVEDV and/or LVESV         | 33 (29.7%)  | none                          | Trivakoglou 2016   |
|                                 | 112  | Prospective     | at admission, 0-3 hours, 6 hours, 12 hours, 24 hours and daily until discharge | TTE, 6 months                           | ≥20% increase in LVEDV                      | 24 (21.4%)  | positive, multivariate        | Urbano-Moral 2012  |
|                                 | 1995 | Retrospective   | unavailable                                                                    | TTE, 3 months, 6 months, 12 months      | ≥20% increase in LVEDV                      | 953 (47.8%) | positive                      | van der Bijl 2020  |
|                                 | 600  | Retrospective   | Within 48 hours of admission                                                   | TTE, 3 months                           | ≥20% increase in LVEDV                      | 150 (25.0%) | positive                      | Lustosa 2020       |
| hs Troponin T                   | 88   | Prospective     | unavailable                                                                    | CMR, 4 months                           | ≥20% increase in LVEDV                      | 11 (12.5%)  | positive, multivariate        | Reindl 2017        |
|                                 | 123  | Prospective     | at admission, 6 hours, 12 hours, daily between day 1 and day 4                 | CMR, 4 months                           | ≥20% increase in LVEDV                      | 16 (13.0%)  | none (admission)              | Reinstadler 2016   |
| Peak hs troponin T              | 143  | Prospective     | unavailable                                                                    | CMR, 4 months                           | ≥15% increase in LVEDV                      | 29 (20%)    | positive, multivariate        | Reindl 2016        |
|                                 | 102  | Prospective     | unavailable                                                                    | CMR, 4 months                           | ≥20% increase in LVEDV                      | 15 (14.7%)  | positive, multivariate        | Reindl 2019        |
|                                 | 123  | Prospective     | at admission and daily between day 1 and day 4                                 | CMR, 4 months                           | ≥20% increase in LVEDV                      | 16 (13.0%)  | positive                      | Reinstadler 2016   |
|                                 | 40   | Prospective     | unavailable                                                                    | CMR, 3 months                           | ≥10% decrease in LVESV (reverse remodeling) | 15 (37.5%)  | positive                      | Grabka 2018        |
| Peak troponin                   | 66   | Prospective     | upon admission and after 6, 12, and 24 hours                                   | TTE, 3 months                           | ≥20% increase in LVEDV                      | 22 (33%)    | positive, none (multivariate) | Chohenek 2011      |
|                                 | 83   | RCT substudy    | unavailable                                                                    | TTE, 3 months, 12 months                | ≥20% increase in LVESV                      | 43 (51.8%)  | borderline (p=0.05)           | Manrique 2016      |
|                                 | 295  | Retrospective   | at admission, 24 hours                                                         | TTE, 6 months                           | ≥20% increase in LVEDV                      | 60 (23.5%)  | positive                      | Turkoglu 2016      |
|                                 | 60   | Not available   | unavailable                                                                    | TTE, 6 months                           | ≥20% increase in LVEDV                      | 14 (23.3%)  | none                          | Wila 2011          |
|                                 | 1237 | Registry        | unavailable                                                                    | TTE, 6 months                           | >10% decrease in LVESV (reverse remodeling) | 468 (37.7%) | positive, multivariate        | Choe 2018          |
| Troponin                        | 55   | Not available   | baseline                                                                       | TTE, 2 months                           | ≥15% increase in LVESV                      | 13 (24%)    | positive                      | Barbato 2013       |
| Peak Creatin Kinase total       | 137  | Not available   | at admission                                                                   | TTE, 12 months                          | ≥20% increase in LVEDV                      | 44 (32%)    | positive                      | Bauters 2007       |
| Creatin Kinase                  | 100  | Not available   | baseline                                                                       | TTE, 6 months                           | ≥20% increase in LVEDV and/or LVESV         | 39 (39%)    | positive                      | Avadalla 2007      |
|                                 | 290  | Prospective     | before discharge (average day 4)                                               | TTE, 6 months                           | increase in LVEDV                           | 146 (50%)   | none                          | Devaux 2012        |
| (84% STEMI)                     |      | Prospective     | day 3-4 (before discharge)                                                     | TTE, 176 days (derivation cohort, n=60) | increase in LVEDV                           | 30 (50%)    | none                          | Devaux 2013        |
| 60 (validation cohort)          |      |                 |                                                                                | CMR, 121 days (validation cohort, n=30) |                                             |             |                               |                    |
|                                 | 216  | Prospective     | day 2                                                                          | TTE, 6 months                           | change in LVEDVI                            | NA          | positive, multivariate        | Lin 2014           |
|                                 | 48   | Not available   | every 6 hours until peak levels                                                | TTE, 6 months                           | ≥15% increase in LVESV                      | 11 (22.9%)  | positive                      | Turan 2012         |
|                                 | 81   | Not available   | on admission then every 8 hours for the first 24 hours then daily until peak   | TTE, 6 months                           | ≥20% increase in LVEDV                      | 33 (40.7%)  | positive                      | Bastawy 2018       |
|                                 | 64   | Matched cohorts | 48h [ICR 24-72]                                                                | CMR, 3 months, 12 months                | >10% increase in LVESV                      | NA          | none                          | Garcia 2019        |
|                                 | 39   | Prospective     | during PCI, 3 hours, 6 hours, 12 hours and/or 24 hours                         | TTE, 6 months                           | ≥20% increase in LVEDV with LVEF<50 %       | 14 (35.9%)  | positive                      | Galeano-Otero 2020 |
| Log Creatin Kinase              | 264  | Not available   | day 2                                                                          | TTE, 6 months                           | >20 mEq increase in LVEDVI                  | unavailable | positive, multivariate        | Lin 2015           |
|                                 | 331  | Prospective     | unavailable                                                                    | TTE, 6 months                           | increase in LVEDVI                          | NA          | positive, multivariate        | Liu 2019           |
| Peak Creatin Kinase (Q-wave MI) | 226  | Prospective     | at discharge (day 3 to day 7)                                                  | TTE, 12 months                          | percent change in LVEDV                     | NA          | positive, multivariate        | Bauters 2013       |
|                                 | 131  | Not available   | at presentation and every 24 h for at least 5 days                             | Left ventriculography, 6 months         | ≥10% increase in LVEDVI                     | 48 (37%)    | none                          | Aoki 2011          |
|                                 | 109  | Retrospective   | repeated measurements within the first 96 hours                                | TTE, 17 months                          | ≥20% increase in LVEDVI                     | 30 (28%)    | none                          | Buono 2011         |
|                                 | 512  | Not available   | baseline                                                                       | TTE, 6 months                           | >10% decrease in LVESV (reverse remodeling) | 252 (49%)   | positive, multivariate        | Carrabba 2012      |
|                                 | 89   | Prospective     | serially                                                                       | CMR, 4 months                           | ≥20% increase in LVEDV                      | 14 (15.7%)  | positive                      | Feinstein 2015     |
|                                 | 36   | Prospective     | unavailable                                                                    | TTE, 6 months                           | >20% increase in LVEDV                      | 13 (36.1%)  | positive                      | Lombardo 2012      |
| 359 (AMI)                       |      | Not available   | at admission                                                                   | TTE, 6 months                           | >10% increase in LVEDV                      | 116 (32.3%) | none                          | Ly 2014            |
| 208                             |      | Not available   | unavailable                                                                    | TTE, 6 months                           | >20% increase in LVEDV                      | 53 (25.5%)  | none                          | Na 2016            |
| 46                              |      | Not available   | unavailable                                                                    | CMR, 12 months                          | ≥20% increase in LVEDV                      | 16 (35%)    | none                          | O'Regan 2012       |
| 75                              |      | Prospective     | unavailable                                                                    | CMR, 6 months                           | >5% increase in LVEDV                       | 22 (32%)    | positive                      | Sugano 2017        |
|                                 | 75   | Prospective     | unavailable                                                                    | TTE, 6 months                           | >20% increase in LVEDV                      | 15 (20%)    | negative                      | Suntyoshi 2017     |

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Table 1

|                |                 |                                                                              |                                 |                                                                                                     |             |                        |                   |
|----------------|-----------------|------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------|-------------|------------------------|-------------------|
| 92             | Not available   | unavailable                                                                  | CMR, 6 months                   | any increase in LVESV                                                                               | 29 (32%)    | positive               | Watabe 2016       |
| 104            | Prospective     | every 4 hours until the values started to decrease                           | TTE, 6 months                   | ≥15% decrease in LVESV (reverse remodeling)                                                         | 56 (53.8%)  | reverse                | Wu 2018           |
| 64             | Matched cohorts | 48h [IQR 24-72]                                                              | CMR, 3 months, 12 months        | >10% increase in LVESV                                                                              | NA          | NA                     | Garcia 2019       |
| 58             | Not available   | unavailable                                                                  | TTE, 6 months                   | change in LVEDV                                                                                     | NA          | NA                     | Hataea 2019       |
| 100            | Not available   | baseline                                                                     | TTE, 6 months                   | ≥20% increase in LVEDV and/or LVESV                                                                 | 39 (39%)    | positive               | Awadalla 2007     |
| 55             | Not available   | baseline                                                                     | TTE, 2 months                   | ≥15% increase in LVESV                                                                              | 13 (24%)    | none                   | Barberato 2013    |
| 39             | RCT             | 4 hours after PCI                                                            | TTE, 3 months                   | >20% increase in LVEDV                                                                              | 13 (33.3%)  | none                   | Ezbieciak 2013    |
| 198            | Not available   | day 5                                                                        | TTE, 12 months                  | >20% increase in LVEDV                                                                              | 56 (28.3%)  | positive               | Liu 2015          |
| 30             | Not available   | at admission, 8 hours, 16 hours, 24 hours                                    | TTE, 1 month, 6 months          | none                                                                                                | NA          | none                   | Radovan 2006      |
| 198            | Prospective     | unavailable                                                                  | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 55 (27.8%)  | positive               | Swiatkiewicz 2012 |
| 48             | Not available   | every 6 hours until peak levels                                              | TTE, 6 months                   | ≥15% increase in LVESV                                                                              | 11 (22.9%)  | positive, multivariate | Turan 2012        |
| 81             | Not available   | on admission then every 8 hours for the first 24 hours then daily until peak | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 33 (40.7%)  | positive               | Bastawy 2018      |
| 57             | Not available   | during PCI                                                                   | TTE, 6 months                   | >20% increase in LVESV                                                                              | 22 (38.6%)  | none                   | Andrzejc 2019     |
| 199            | Prospective     | unavailable                                                                  | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 49 (24.6%)  | positive               | Chu 2020          |
| 109            | Retrospective   | repeated measurements within the first 96 hours                              | TTE, 17 months                  | >20% increase in LVEDV                                                                              | 30 (28%)    | none                   | Buono 2011        |
| 131            | Not available   | every four hours after hospital admission for three days                     | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 42 (32%)    | positive, multivariate | Choi 2013         |
| 478            | Not available   | overnight after admission                                                    | TTE, 12 months                  | ≥15% increase in LVEDV                                                                              | 226 (47.3%) | positive, multivariate | Fan 2017          |
| 54             | Not available   | immediately, 8 hours, 16 hours                                               | TTE, 3 months, 6 months         | >15% increase in LVESV (6 months)                                                                   | 19 (35.2%)  | none                   | Hsiao 2016        |
| 97 (61 % STEM) | Prospective     | at first 3 days                                                              | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 24 (32.9%)  | positive               | Hsu 2017          |
| 234            | Prospective     | unavailable                                                                  | CMR, 6 months                   | dilated LVESV according to accepted reference values according to gender, age and body surface area | 94 (40.2%)  | positive               | Husser 2013       |
| 35             | Prospective     | at admission                                                                 | TTE, 2 months, 12 months        | >20% increase in LVEDV (2 months)                                                                   | 14 (40%)    | none                   | Khurelsukh 2016   |
| 262            | Not available   | unavailable                                                                  | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 66 (25.2%)  | positive               | Kim 2017          |
| 105            | Prospective     | SPECT, 44 months                                                             | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 25 (23.8%)  | positive               | Sato 2006         |
| 75             | Prospective     | unavailable                                                                  | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 15 (20%)    | negative               | Suntyoshi 2017    |
| 111            | Prospective     | baseline, 6 hours, 24 hours                                                  | TTE, 6 months                   | >20% increase in LVEDV and/or LVESV                                                                 | 33 (29.7%)  | none                   | Tiryakoglu 2016   |
| 255            | Retrospective   | at admission, 24 hours                                                       | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 60 (23.5%)  | positive               | Turkoglu 2016     |
| 1237           | Registry        | unavailable                                                                  | TTE, 6 months                   | >10% decrease in LVESV (reverse remodeling)                                                         | 466 (37.7%) | reverse                | Choe 2018         |
| 87             | Prospective     | on admission and every 12 hours for at least 72 hours after PCI              | TTE, 6 months                   | >15% increase in LVESV                                                                              | 44 (50.6%)  | positive               | Spinelli 2018     |
| 104            | Prospective     | every 4 hours until the values started to decrease                           | TTE, 6 months                   | ≥15% decrease in LVESV (reverse remodeling)                                                         | 56 (53.8%)  | reverse                | Wu 2018           |
| 40             | Prospective     | unavailable                                                                  | CMR, 3 months                   | >10% decrease in LVESV (reverse remodeling)                                                         | 15 (37.5%)  | none                   | Grabka 2018       |
| 58             | Not available   | unavailable                                                                  | TTE, 6 months                   | change in LVEDV                                                                                     | NA          | NA                     | Hataea 2019       |
| 82             | Retrospective   | unavailable                                                                  | CMR, 7 months                   | >20% increase in LVEDV                                                                              | 20 (24.4%)  | positive               | Cha 2019          |
| 199            | Prospective     | unavailable                                                                  | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 49 (24.6%)  | positive               | Chu 2020          |
| 83             | Prospective     | baseline                                                                     | TTE, 6 months                   | ≥10% increase in LVEDD or LVESD                                                                     | 26 (31%)    | positive               | Cogni 2013        |
| 35             | Prospective     | at admission                                                                 | TTE, 2 months, 12 months        | >20% increase in LVEDV (2 months)                                                                   | 14 (40%)    | none                   | Khurelsukh 2016   |
| 213            | Retrospective   | baseline                                                                     | TTE, 6 months                   | ≥15% increase in LVESV                                                                              | 44 (21%)    | positive               | Alate 2014        |
| 218            | Not available   | at admission                                                                 | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 52 (24%)    | positive, multivariate | Araszkiewicz 2014 |
| 42             | Not available   | baseline                                                                     | TTE, 3 months                   | >15% increase in LVESV                                                                              | 13 (31%)    | positive               | Bonios 2014       |
| 80             | Prospective     | at baseline and every six hours until their levels started to decrease       | TTE, 6 months                   | ≥15% increase in LVEDV and/or LVESV                                                                 | 41 (51.3%)  | positive, multivariate | Farah 2013        |
| 964            | Prospective     | unavailable                                                                  | TTE, 6 months                   | >20% increase in LVEDV                                                                              | 296 (30.7%) | positive               | Joyce 2013        |
| 78             | Not available   | unavailable                                                                  | Left ventriculography, 6 months | >10% increase in LVEDV                                                                              | 36 (44.9%)  | positive               | Obata 2020        |
| 600            | Retrospective   | within 48 hours of admission                                                 | TTE, 3 months                   | >20% increase in LVEDV                                                                              | 150 (25.0%) | positive               | Lustosa 2020      |

Table 1

|                                |     |               |                                                                        |                |                                     |            |                  |                  |
|--------------------------------|-----|---------------|------------------------------------------------------------------------|----------------|-------------------------------------|------------|------------------|------------------|
| Creatin phospho kinase-MB      | 83  | Prospective   | baseline                                                               | TTE, 6 months  | ≥10% increase in LVEDD or LVESD     | 26 (31%)   | positive         | Cogni 2013       |
| Peak Creatin phospho kinase-MB | 135 | Not available | baseline                                                               | TTE, 6 months  | ≥20% increase in LVEDV              | 28 (21%)   | positive         | Alm 2013         |
|                                | 80  | Prospective   | at baseline and every six hours until their levels started to decrease | TTE, 6 months  | ≥15% increase in LVEDV and/or LVESV | 41 (51.3%) | positive         | Farah 2013       |
|                                | 208 | Not available | repeated measurements within the first 96 hours                        | TTE, 6 months  | ≥20% increase in LVEDV              | 53 (25.5%) | positive         | Na 2016          |
| Peak lactate dehydrogenase     | 109 | Retrospective | repeated measurements within the first 96 hours                        | TTE, 17 months | ≥20% increase in LVEDV              | 30 (28%)   | positive         | Buono 2011       |
|                                | 123 | Prospective   | at admission and daily between day 1 and day 4                         | CMR, 4 months  | ≥20% increase in LVEDV              | 16 (13.0%) | positive         | Reinstadler 2016 |
| Lactate dehydrogenase          | 123 | Prospective   | at admission and daily between day 1 and day 4                         | CMR, 4 months  | ≥20% increase in LVEDV              | 16 (13.0%) | none (admission) | Reinstadler 2016 |
| Peak myoglobin                 | 109 | Retrospective | repeated measurements within the first 96 hours                        | TTE, 17 months | ≥20% increase in LVEDV              | 30 (28%)   | none             | Buono 2011       |

Table 2

| Table 2                                | sample size     | design        | biomarker assessment                               | follow-up imaging                   | definition of LVR                            | LVR                 | correlation                       | reference     |
|----------------------------------------|-----------------|---------------|----------------------------------------------------|-------------------------------------|----------------------------------------------|---------------------|-----------------------------------|---------------|
| NT-pro ANP                             | 71              | Prospective   | Baseline, 3 months                                 | TTE, 3 months, 12 months, 24 months | LVEDVI increase >20 ml/m <sup>2</sup>        | 12 (17%)            | positive, multivariate (baseline) | Hole 2004     |
| Atrial natriuretic peptide             | 33              | Not available | at admission, 1 month, 3 months                    | Left ventriculography, 3 months     | ≥8% increase in LVEDVI                       | 14 (42.4%)          | none                              | Yoshiomi 1998 |
| Hematocrit                             | 104             | Prospective   | day 1, day 3, day 5 and day 7                      | TTE, 6 months                       | ≥15% decrease in LVEDVI (reverse remodeling) | 56 (53.8%), reverse | none                              | Wu 2018       |
| Platelets                              | 255             | Retrospective | at admission, 24 hours                             | TTE, 6 months                       | ≥20% increase in LVEDVI                      | 60 (23.5%)          | negative                          | Türkoglu 2016 |
| Mean platelet volume                   | 255             | Retrospective | at admission, 24 hours                             | TTE, 6 months                       | ≥20% increase in LVEDVI                      | 60 (23.5%)          | positive                          | Türkoglu 2016 |
| Peak peripheral blood mononuclear cell | 131             | Not available | at presentation and every 24 h for at least 5 days | Left ventriculography, 6 months     | ≥10% increase in LVEDVI                      | 48 (37%)            | positive, multivariate            | Aoki 2011     |
| Fibrinogen                             | 131             | Not available | at presentation                                    | Left ventriculography, 6 months     | ≥10% increase in LVEDVI                      | 48 (37%)            | positive                          | Aoki 2011     |
| TNF-α                                  | 33 (AMI)        | Not available | day 1, day 7 and day 14                            | Left ventriculography, 6 months     | unavailable                                  | NA                  | none                              | Kondo 2009    |
| Interleukin-8                          | 258             | RCT substudy  | before and immediately after PCI, day 1            | CMR, 4 months                       | an increase in LVEDVI >10 ml/m <sup>2</sup>  | unavailable         | none                              | Shetelig 2018 |
| MMP-1                                  | 226 (Q-wave MI) | Prospective   | at discharge (day 3 to day 7)                      | TTE, 12 months                      | >20% increase in LVEDVI                      | 87 (38%)            | none                              | Ferin 2013    |
| MMP-7                                  | 106             | RCT substudy  | early after PCI and at days 1, 7                   | TTE, 6 months                       | unavailable                                  | NA                  | none                              | Cerisano 2015 |
|                                        | 32 (84 % STEMI) | Prospective   | at enrollment, days 2 to 5                         | TTE, 3 months, 6 months             | none                                         | NA                  | none                              | Webb 2006     |
| TIMP-3                                 | 106             | RCT substudy  | early after PCI and at days 1, 7                   | TTE, 6 months                       | unavailable                                  | NA                  | none                              | Cerisano 2015 |
| TIMP-4                                 | 106             | RCT substudy  | early after PCI and at days 1, 7                   | TTE, 6 months                       | unavailable                                  | NA                  | none                              | Cerisano 2015 |
|                                        | 226 (Q-wave MI) | Prospective   | at discharge (day 3 to day 7)                      | TTE, 12 months                      | >20% increase in LVEDVI                      | 87 (38%)            | none                              | Ferin 2013    |
|                                        | 42              | Not available | prior to PCI, day 2, week 1                        | CMR, 2 months and 12 months         | none                                         | NA                  | none                              | Manhenke 2014 |

Table 3

| Table 3                         | sample size                                                         | design          | biomarker assessment                                                              | follow-up imaging                  | definition of LVR                           | LVR         | correlation            | reference                |
|---------------------------------|---------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------------|------------------------------------|---------------------------------------------|-------------|------------------------|--------------------------|
| Creatinin                       | 131                                                                 | Not available   | at presentation                                                                   | Left ventriculography, 6 months    | ≥10% increase in LVEDVI                     | 48 (37%)    | none                   | Aoki 2011                |
|                                 | 62                                                                  | Prospective     | within 24 hours                                                                   | TTE, 1 month                       | ≥20% increase in LVEDV                      | 16 (26%)    | none                   | Abdel Hamid 2016         |
|                                 | 55                                                                  | Not available   | baseline                                                                          | TTE, 2 months                      | ≥15% increase in LVEDV                      | 13 (24%)    | none                   | Barbarato 2013           |
|                                 | 42                                                                  | Not available   | baseline                                                                          | TTE, 3 months                      | >15% increase in LVEDV                      | 13 (31%)    | none                   | Boniss 2014              |
|                                 | 109                                                                 | Retrospective   | once daily during hospitalization                                                 | TTE, 17 months                     | ≥20% increase in LVEDVI                     | 30 (28%)    | positive               | Buono 2011               |
|                                 | 92                                                                  | Prospective     | baseline                                                                          | TTE, 6 months                      | ≥15% increase in LVEDV                      | 26 (28.2%)  | none                   | Di Tano 2017             |
|                                 | 97                                                                  | Prospective     | at admission                                                                      | TTE, 12 months                     | >20% increase in LVEDV                      | 21 (21.6%)  | none                   | Dominquez-Rodriguez 2011 |
|                                 | 89                                                                  | Prospective     | unavailable                                                                       | CMR, 4 months                      | ≥20% increase in LVEDV                      | 14 (15.7%)  | none                   | Feistritzer 2015         |
|                                 | 208                                                                 | Not available   | unavailable                                                                       | TTE, 6 months                      | >20% increase in LVEDV                      | 53 (25.5%)  | none                   | Na 2016                  |
|                                 | 88                                                                  | Prospective     | unavailable                                                                       | CMR, 4 months                      | ≥20% increase in LVEDV                      | 11 (12.5%)  | none                   | Reindl 2017              |
| estimated glomerular filtration | 198                                                                 | Prospective     | unavailable                                                                       | TTE, 6 months                      | >20% increase in LVEDV                      | 55 (27.8%)  | none                   | Swiatkiewicz 2012        |
|                                 | 255                                                                 | Retrospective   | at admission, 24 hours                                                            | TTE, 6 months                      | ≥20% increase in LVEDV                      | 60 (23.5%)  | none                   | Turkoglu 2016            |
|                                 | 60                                                                  | Not available   | unavailable                                                                       | TTE, 6 months                      | ≥20% increase in LVEDV                      | 14 (23.3%)  | none                   | Wita 2011                |
|                                 | 104                                                                 | Prospective     | before and after PCI                                                              | TTE, 6 months                      | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | none                   | Wu 2018                  |
|                                 | 40                                                                  | Prospective     | unavailable                                                                       | CMR, 3 months                      | ≥10% decrease in LVESV (reverse remodeling) | 15 (37.5%)  | none                   | Grabka 2018              |
|                                 | 64                                                                  | Matched cohorts | 48h [IQR 24;72]                                                                   | CMR, 3 months, 12 months           | >10% increase in LVESV                      | NA          | none                   | Garcia 2019              |
|                                 | 58                                                                  | Not available   | unavailable                                                                       | TTE, 6 months                      | change in LVEDV                             | NA          | none                   | Hataa 2019               |
|                                 | 57                                                                  | Not available   | during PCI                                                                        | TTE, 6 months                      | ≥20% increase in LVESV                      | 22 (38.6%)  | none                   | Andrejic 2019            |
|                                 | 109                                                                 | Retrospective   | once daily during hospitalization                                                 | TTE, 17 months                     | ≥20% increase in LVEDVI                     | 30 (28%)    | negative               | Buono 2011               |
|                                 | 89                                                                  | Prospective     | unavailable                                                                       | CMR, 4 months                      | ≥20% increase in LVEDV                      | 14 (15.7%)  | none                   | Feistritzer 2015         |
| Uric acid                       | 54                                                                  | Not available   | immediately, 8 hours, 16 hours                                                    | TTE, 3 months, 6 months            | >15% increase in LVESV (6 months)           | 19 (35.2%)  | none                   | Hatao 2016               |
|                                 | 964                                                                 | Prospective     | unavailable                                                                       | TTE, 6 months                      | ≥20% increase in LVEDV                      | 296 (30.7%) | none                   | Joyce 2013               |
|                                 | 198                                                                 | Not available   | day 5                                                                             | TTE, 12 months                     | ≥20% increase in LVEDV                      | 56 (28.3%)  | negative, multivariate | Liu 2015                 |
|                                 | 143                                                                 | Prospective     | unavailable                                                                       | CMR, 4 months                      | ≥15% increase in LVEDV                      | 29 (20%)    | none                   | Reindl 2016              |
|                                 | 110                                                                 | Prospective     | unavailable                                                                       | TTE, 3 months                      | ≥20% increase in LVEDV                      | 26 (23.6%)  | none                   | Xu 2017                  |
|                                 | 1237                                                                | Registry        | unavailable                                                                       | TTE, 6 months                      | >10% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | reverse                | Choe 2018                |
|                                 | 1995                                                                | Retrospective   | unavailable                                                                       | TTE, 3 months, 6 months, 12 months | ≥20% increase in LVEDV                      | 953 (47.8%) | positive               | van der Bijl 2020        |
|                                 | 199                                                                 | Prospective     | unavailable                                                                       | TTE, 6 months                      | >20% increase in LVEDV                      | 49 (24.6%)  | none                   | Chiu 2020                |
|                                 | 97 (61 % STEM)                                                      | Prospective     | unavailable                                                                       | TTE, 6 months                      | >20% increase in LVEDV                      | 24 (32.9%)  | none                   | Hsu 2017                 |
|                                 | 131                                                                 | Not available   | at presentation                                                                   | Left ventriculography, 6 months    | ≥10% increase in LVEDVI                     | 48 (37%)    | positive, multivariate | Aoki 2011                |
| Fasting plasma glucose          | 109                                                                 | Retrospective   | once daily during hospitalization in the morning of the first day after admission | TTE, 17 months                     | ≥20% increase in LVEDVI                     | 30 (28%)    | none                   | Buono 2011               |
|                                 | 104                                                                 | Prospective     | unavailable                                                                       | TTE, 6 months                      | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | reverse                | Wu 2018                  |
|                                 | 69                                                                  | Prospective     | at admission                                                                      | CMR, 7 months                      | ≥20% increase in LVEDVI                     | 18 (26.1%)  | none                   | Gohbara 2015             |
|                                 | 143                                                                 | Prospective     | unavailable                                                                       | CMR, 4 months                      | ≥15% increase in LVEDV                      | 29 (20%)    | none                   | Reindl 2016              |
|                                 | 104                                                                 | Prospective     | in the morning of the first day after admission                                   | TTE, 6 months                      | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | reverse                | Wu 2018                  |
|                                 | 58                                                                  | Not available   | unavailable                                                                       | TTE, 6 months                      | change in LVEDV                             | NA          | none                   | Hataa 2019               |
|                                 | 69                                                                  | Prospective     | 24-h period of 11±6 days                                                          | CMR, 7 months                      | ≥20% increase in LVEDVI                     | 18 (26.1%)  | positive, multivariate | Gohbara 2015             |
|                                 | 485                                                                 | Retrospective   | at discharge                                                                      | TTE, 12 months                     | none                                        | NA          | positive               | Yang 2019                |
|                                 | mean amplitude of glycemic excursions                               |                 |                                                                                   |                                    |                                             |             |                        |                          |
|                                 | homeostasis model assessment-estimated insulin resistance (HOMA-IR) |                 |                                                                                   |                                    |                                             |             |                        |                          |
| Bilirubin                       | 145                                                                 | Prospective     | the morning after admission                                                       | CMR, 6 months                      | ≥20% increase in LVEDV                      | 42 (29.2%)  | none                   | Miranda 2016             |
|                                 | 123                                                                 | Prospective     | at admission and daily between day 1 and day 4                                    | CMR, 4 months                      | ≥20% increase in LVEDV                      | 16 (13.0%)  | none                   | Reinstadler 2016         |
|                                 | 123                                                                 | Prospective     | at admission and daily between day 1 and day 4                                    | CMR, 4 months                      | ≥20% increase in LVEDV                      | 16 (13.0%)  | none                   | Reinstadler 2016         |
|                                 | 123                                                                 | Prospective     | at admission and daily between day 1 and day 4                                    | CMR, 4 months                      | ≥20% increase in LVEDV                      | 16 (13.0%)  | positive               | Reinstadler 2016         |

Table 3

| Peak AST  | 123 | Prospective | at admission and daily between day 1 and day 4 | CMR, 4 months | ≥20% increase in LVEDV | 16 (13.0%) | positive               | Reinstadler 2016 |
|-----------|-----|-------------|------------------------------------------------|---------------|------------------------|------------|------------------------|------------------|
| Calcium   | 88  | Prospective | unavailable                                    | CMR, 4 months | ≥20% increase in LVEDV | 11 (12.5%) | none                   | Reindl 2017      |
| Phosphate | 88  | Prospective | unavailable                                    | CMR, 4 months | ≥20% increase in LVEDV | 11 (12.5%) | none                   | Reindl 2017      |
| TSH       | 102 | Prospective | day 1                                          | CMR, 4 months | ≥20% increase in LVEDV | 15 (14.7%) | negative, multivariate | Reindl 2019      |

Table 4

| Table 4                              | sample size | design        | biomarker assessment                                    | follow-up imaging               | definition of LVR                           | LVR         | correlation | reference                |
|--------------------------------------|-------------|---------------|---------------------------------------------------------|---------------------------------|---------------------------------------------|-------------|-------------|--------------------------|
| Total cholesterol                    | 131         | Not available | at presentation                                         | Left ventriculography, 6 months | ≥10% increase in LVEDVI                     | 48 (37%)    | none        | Aoki 2011                |
|                                      | 109         | Retrospective | the day after admission, after a 12-hour overnight fast | TTE, 17 months                  | ≥20% increase in LVEDVI                     | 30 (28%)    | none        | Buono 2011               |
|                                      | 97          | Prospective   | at admission                                            | TTE, 12 months                  | >20% increase in LVEDV                      | 21 (21.6%)  | none        | Dominguez-Rodriguez 2011 |
|                                      | 89          | Prospective   | unavailable                                             | CMR, 4 months                   | ≥20% increase in LVEDV                      | 14 (15.7%)  | none        | Felstizer 2015           |
|                                      | 208         | Not available | unavailable                                             | TTE, 6 months                   | >20% increase in LVEDV                      | 53 (25.5%)  | none        | Na 2016                  |
|                                      | 255         | Retrospective | at admission, 24 hours                                  | TTE, 6 months                   | ≥20% increase in LVEDV                      | 60 (23.5%)  | none        | Turkoğlu 2016            |
|                                      | 104         | Prospective   | in the morning of the first day after admission         | TTE, 6 months                   | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | reverse     | Wu 2018                  |
|                                      | 98          | Not available | unavailable                                             | TTE, 6 months                   | change in LVEDV                             | NA          | NA          | Hataza 2019              |
|                                      | 57          | Not available | during PCI                                              | TTE, 6 months                   | ≥20% increase in LVESV                      | 22 (38.6%)  | none        | Andrejic 2019            |
|                                      | 109         | Retrospective | the day after admission, after a 12-hour overnight fast | TTE, 17 months                  | ≥20% increase in LVEDVI                     | 30 (28%)    | positive    | Buono 2011               |
| High-density lipoprotein cholesterol | 198         | Prospective   | unavailable                                             | TTE, 6 months                   | >20% increase in LVEDV                      | 55 (27.8%)  | none        | Swiatkiewicz 2012        |
|                                      | 255         | Retrospective | at admission, 24 hours                                  | TTE, 6 months                   | ≥20% increase in LVEDV                      | 60 (23.5%)  | none        | Turkoğlu 2016            |
|                                      | 104         | Prospective   | in the morning of the first day after admission         | TTE, 6 months                   | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | reverse     | Wu 2018                  |
|                                      | 98          | Not available | unavailable                                             | TTE, 6 months                   | change in LVEDV                             | NA          | none        | Hataza 2019              |
|                                      | 57          | Not available | during PCI                                              | TTE, 6 months                   | ≥20% increase in LVESV                      | 22 (38.6%)  | none        | Andrejic 2019            |
|                                      | 109         | Retrospective | the day after admission, after a 12-hour overnight fast | TTE, 17 months                  | ≥20% increase in LVEDVI                     | 30 (28%)    | none        | Buono 2011               |
| Low-density lipoprotein cholesterol  | 198         | Prospective   | unavailable                                             | TTE, 6 months                   | >20% increase in LVEDV                      | 55 (27.8%)  | none        | Swiatkiewicz 2012        |
|                                      | 255         | Retrospective | at admission, 24 hours                                  | TTE, 6 months                   | ≥20% increase in LVEDV                      | 60 (23.5%)  | none        | Turkoğlu 2016            |
|                                      | 1237        | Registry      | unavailable                                             | TTE, 6 months                   | >10% decrease in LVESV (reverse remodeling) | 486 (37.7%) | reverse     | Choe 2018                |
|                                      | 104         | Prospective   | in the morning of the first day after admission         | TTE, 6 months                   | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | reverse     | Wu 2018                  |
|                                      | 98          | Not available | unavailable                                             | TTE, 6 months                   | change in LVEDV                             | NA          | none        | Hataza 2019              |
|                                      | 57          | Not available | during PCI                                              | TTE, 6 months                   | ≥20% increase in LVESV                      | 22 (38.6%)  | none        | Andrejic 2019            |
|                                      | 131         | Not available | at presentation                                         | Left ventriculography, 6 months | ≥10% increase in LVEDVI                     | 48 (37%)    | none        | Aoki 2011                |
|                                      | 109         | Retrospective | the day after admission, after a 12-hour overnight fast | TTE, 17 months                  | ≥20% increase in LVEDVI                     | 30 (28%)    | none        | Buono 2011               |
|                                      | 208         | Not available | unavailable                                             | TTE, 6 months                   | >20% increase in LVEDV                      | 53 (25.5%)  | none        | Na 2016                  |
|                                      | 198         | Prospective   | unavailable                                             | TTE, 6 months                   | >20% increase in LVEDV                      | 55 (27.8%)  | none        | Swiatkiewicz 2012        |
| Triglycerides                        | 255         | Retrospective | at admission, 24 hours                                  | TTE, 6 months                   | ≥20% increase in LVEDV                      | 60 (23.5%)  | none        | Turkoğlu 2016            |
|                                      | 98          | Not available | unavailable                                             | TTE, 6 months                   | change in LVEDV                             | NA          | none        | Hataza 2019              |
|                                      | 57          | Not available | during PCI                                              | TTE, 6 months                   | ≥20% increase in LVESV                      | 22 (38.6%)  | none        | Andrejic 2019            |
|                                      | 131         | Not available | at presentation                                         | Left ventriculography, 6 months | ≥10% increase in LVEDVI                     | 48 (37%)    | none        | Aoki 2011                |
| Triglycerides                        | 131         | Not available | at presentation                                         | Left ventriculography, 6 months | ≥10% increase in LVEDVI                     | 48 (37%)    | none        | Aoki 2011                |
|                                      | 109         | Retrospective | the day after admission, after a 12-hour overnight fast | TTE, 17 months                  | ≥20% increase in LVEDVI                     | 30 (28%)    | none        | Buono 2011               |
|                                      | 208         | Not available | unavailable                                             | TTE, 6 months                   | >20% increase in LVEDV                      | 53 (25.5%)  | none        | Na 2016                  |
|                                      | 198         | Prospective   | unavailable                                             | TTE, 6 months                   | >20% increase in LVEDV                      | 55 (27.8%)  | none        | Swiatkiewicz 2012        |
|                                      | 255         | Retrospective | at admission, 24 hours                                  | TTE, 6 months                   | ≥20% increase in LVEDV                      | 60 (23.5%)  | none        | Turkoğlu 2016            |
|                                      | 98          | Not available | unavailable                                             | TTE, 6 months                   | change in LVEDV                             | NA          | none        | Hataza 2019              |
| Triglycerides                        | 57          | Not available | during PCI                                              | TTE, 6 months                   | ≥20% increase in LVESV                      | 22 (38.6%)  | none        | Andrejic 2019            |

Table 5

| microRNAs                                  | sample size                                         | design        | biomarker assessment                     | follow-up imaging                                                                        | definition of LVR                           | LVR         | correlation                                                    | reference                |
|--------------------------------------------|-----------------------------------------------------|---------------|------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------|-------------|----------------------------------------------------------------|--------------------------|
| miR-133a                                   | 226 (Q-wave MI)                                     | Prospective   | at discharge (day 3 to day 7)            | TTE, 12 months                                                                           | percent change in LVEDV                     | NA          | positive, multivariate                                         | Bauters 2013             |
| miR-423-5p                                 | 226 (Q-wave MI)                                     | Prospective   | at discharge (day 3 to day 7)            | TTE, 12 months                                                                           | percent change in LVEDV                     | NA          | positive, multivariate                                         | Bauters 2013             |
| miR-150                                    | 60 (derivation cohort)<br>30 (validation cohort)    | Prospective   | day 3-4 (before discharge)               | TTE, 176 days<br>(derivation cohort, n=60)<br>CMR, 121 days<br>(validation cohort, n=30) | increase in LVEDV                           | 30 (50%)    | negative                                                       | Devaux 2013              |
| miR-1                                      | 44                                                  | RCT substudy  | day 4, day 9                             | CMR, 6 months                                                                            | absolute change of LVEDV                    | NA          | none                                                           | Grabmaier 2017           |
| miR-21                                     | 44                                                  | RCT substudy  | day 4, day 9                             | CMR, 6 months                                                                            | absolute change of LVEDV                    | NA          | none                                                           | Grabmaier 2017           |
| miR-29b                                    | 44                                                  | RCT substudy  | day 4, day 9                             | CMR, 6 months                                                                            | absolute change of LVEDV                    | NA          | negative (day 9)                                               | Grabmaier 2017           |
| miR-92a                                    | 44                                                  | RCT substudy  | day 4, day 9                             | CMR, 6 months                                                                            | absolute change of LVEDV                    | NA          | negative (day 9)                                               | Grabmaier 2017           |
| miR-21                                     | 198                                                 | Not available | day 5                                    | TTE, 12 months                                                                           | ≥20% increase in LVEDV                      | 56 (28.3%)  | positive, multivariate                                         | Liu 2015                 |
| miR-146a                                   | 198                                                 | Not available | day 5                                    | TTE, 12 months                                                                           | ≥20% increase in LVEDV                      | 56 (28.3%)  | positive, multivariate                                         | Liu 2015                 |
| miR-208b                                   | 359 (AMI)                                           | Not available | at admission                             | TTE, 6 months                                                                            | >10% increase in LVEDV                      | 116 (32.3%) | negative                                                       | LV 2014                  |
| miR-34a                                    | 359 (AMI)                                           | Not available | at admission                             | TTE, 6 months                                                                            | >10% increase in LVEDV                      | 116 (32.3%) | negative                                                       | LV 2014                  |
| miR-1254                                   | 70                                                  | Prospective   | at admission                             | CMR, 6 months                                                                            | none                                        | NA          | variable (negative regarding changes in LVESV, none otherwise) | de Gonzalo-Calvo 2018    |
| <b>Others</b>                              |                                                     |               |                                          |                                                                                          |                                             |             |                                                                |                          |
| ADAMTS-7                                   | 104                                                 | Prospective   | day 1, day 3, day 7                      | TTE, 6 months                                                                            | ≥15% decrease in LVESV (reverse remodeling) | 56 (53.8%)  | variable (positive day 7, none otherwise)                      | Wu 2018                  |
| Adiponectin                                | 75                                                  | Not available | the next day after admission             | TTE, 12 months                                                                           | ≥20% increase in LVEDV                      | 15 (20%)    | negative, multivariate                                         | Piesztreniewicz 2010     |
| Aortic CD34+<br>CD45dimKR+<br>cells levels | 54                                                  | Prospective   | during PCI                               | TTE, 12 months                                                                           | ≥20% increase in LVEDV                      | NA          | none                                                           | Porto 2013               |
| autoantibody against cardiac troponin-I    | 478                                                 | Not available | overnight after admission                | TTE, 12 months                                                                           | ≥15% increase in LVEDV                      | 226 (47.3%) | positive, multivariate                                         | Fan 2017                 |
| blood coagulation factor XIII              | 75                                                  | Prospective   | day 1, day 2, day 3, day 5, day 7, day 9 | CMR, 12 months                                                                           | none                                        | NA          | none                                                           | Freij 2020               |
| Caesatin                                   | 31 (STEMI 67% of the initial cohort of 95 patients) | Prospective   | at admission, day 3 and day 7            | TTE, 3 months                                                                            | >20% increase in LVEDV                      | 7 (22.6%)   | positive                                                       | Meng 2013                |
| Circulating endothelial cells              | 62                                                  | Prospective   | within 24 hours                          | TTE, 1 month                                                                             | ≥20% increase in LVEDV                      | 16 (26%)    | positive                                                       | Abdel Hamid 2016         |
| double-stranded deoxyribonucleic acid      | 272                                                 | RCT substudy  | before and immediately after PCI, day 1  | CMR, 4 months                                                                            | change in LVEDV or LVESV                    | NA          | none                                                           | Helseth 2019             |
| endothelial nitric oxide synthase          | 62                                                  | Prospective   | within 24 hours                          | TTE, 1 month                                                                             | ≥20% increase in LVEDV                      | 16 (26%)    | none                                                           | Abdel Hamid 2016         |
| gene expression Fetuin-A                   | 89                                                  | Prospective   | 48 hours                                 | CMR, 4 months                                                                            | ≥20% increase in LVEDV                      | 14 (15.7%)  | negative, multivariate                                         | Festritzer 2015          |
| FGF-23                                     | 88                                                  | Prospective   | day 2                                    | CMR, 4 months                                                                            | ≥20% increase in LVEDV                      | 11 (12.5%)  | positive, multivariate                                         | Reindl 2017              |
| Ficolin-2                                  | 55                                                  | RCT substudy  | day 1-2, day 4, day 7                    | CMR, 6 months                                                                            | none                                        | NA          | none                                                           | Schoos 2013              |
| Ficolin-3                                  | 55                                                  | RCT substudy  | day 1-2, day 4, day 7                    | CMR, 6 months                                                                            | none                                        | NA          | none                                                           | Schoos 2013              |
| Granzyme B                                 | 33 (AMI)                                            | Not available | day 1, day 7                             | Left ventriculography, 6 months                                                          | unavailable                                 | NA          | none                                                           | Kondo 2009               |
| Growth Arrest-Specific 6 protein           | 227                                                 | Prospective   | day 1, day 7                             | CMR, 6 months                                                                            | ≥20% increase in LVEDV                      | 29 (16%)    | none                                                           | Cadenave 2019            |
| Growth-differentiation factor 15           | 97                                                  | Prospective   | at admission                             | TTE, 12 months                                                                           | >20% increase in LVEDV                      | 21 (21.6%)  | positive, multivariate                                         | Dominguez-Rodriguez 2011 |
| Hear t-type fatty acid binding protein     | 216                                                 | Prospective   | day 2                                    | TTE, 6 months                                                                            | change in LVEDV                             | NA          | none                                                           | Lin 2014                 |
| interleukin-6                              | 48                                                  | Prospective   | day 2, day 7                             | CMR, 1 month and 3 months                                                                | none                                        | NA          | none                                                           | Mather 2013              |
| interleukin-10                             | 54                                                  | Prospective   | during PCI                               | TTE, 12 months                                                                           | ≥20% increase in LVEDV                      | NA          | none                                                           | Porto 2013               |
| CD45dimKR+ cells levels                    | 255                                                 | Retrospective | at admission, 24 hours                   | TTE, 6 months                                                                            | ≥20% increase in LVEDV                      | 60 (23.5%)  | positive, multivariate                                         | Turkdogu 2016            |
| M30                                        | 255                                                 | Retrospective | at admission, 24 hours                   | TTE, 6 months                                                                            | ≥20% increase in LVEDV                      | 60 (23.5%)  | positive                                                       | Turkdogu 2016            |
| M65                                        | 255                                                 | Retrospective | at admission, 24 hours                   | TTE, 6 months                                                                            | ≥20% increase in LVEDV                      | 60 (23.5%)  | negative                                                       | Turkdogu 2016            |
| M65M30                                     | 255                                                 | Retrospective | at admission, 24 hours                   | TTE, 6 months                                                                            | ≥20% increase in LVEDV                      | 60 (23.5%)  | negative                                                       | Turkdogu 2016            |
| Mannose-binding lectin                     | 55                                                  | RCT substudy  | day 1-2, day 4, day 7                    | CMR, 6 months                                                                            | none                                        | NA          | none                                                           | Schoos 2013              |
| miR-1                                      | 55                                                  | RCT substudy  | day 1-2, day 4, day 7                    | CMR, 6 months                                                                            | none                                        | NA          | none                                                           | Schoos 2013              |
| miR-1                                      | 55                                                  | RCT substudy  | day 1-2, day 4, day 7                    | CMR, 6 months                                                                            | none                                        | NA          | none                                                           | Schoos 2013              |
| melanin                                    | 161 (AMI)                                           | Prospective   | at admission                             | TTE, 12 months                                                                           | >20% increase in LVEDV                      | 24 (14.9%)  | negative, multivariate                                         | Dominguez-Rodriguez 2012 |

Table 5

|                                                      |                 |               |                                         |                                 |                                |             |                                         |                          |
|------------------------------------------------------|-----------------|---------------|-----------------------------------------|---------------------------------|--------------------------------|-------------|-----------------------------------------|--------------------------|
| neopterin                                            | 108             | Prospective   | before primary PCI during PCI           | TTE, 12 months                  | >20% increase in LVEDV         | 21 (19%)    | positive, multivariate                  | Dominquez-Rodriguez 2010 |
| neopterin                                            | 68              | Prospective   | during PCI                              | TTE, 7 months                   | none                           | NA          | none                                    | Legallois 2020           |
| Oxidative Stress Index                               | 255             | Retrospective | at admission, 24 hours                  | TTE, 6 months                   | ≥20% increase in LVEDV         | 60 (23.5%)  | positive, multivariate                  | Turkoglu 2016            |
| Peak adenosine                                       | 58              | Not available | day 0, day 1, day 7                     | TTE, 6 months                   | change in LVEDV                | NA          | negative                                | Haasa 2019               |
| Peak tenascin-C                                      | 105             | Prospective   | unavailable                             | SPECT, 44 months                | ≥20% increase in LVEDV         | 25 (23.8%)  | positive                                | Sato 2006                |
| PGC-1α                                               | 31              | Prospective   | at admission and at 72 hours            | CMR, 6 months                   | >10% increase in LVEDV         | 15 (48.4%)  | positive (increase at 72 hours)         | Fabregat-Andre 2015      |
| serum connective tissue                              | 42              | Prospective   | Day 2, week 1                           | CMR, 2 months and 12 months     | none                           | NA          | variable                                | Graving 2012             |
| growth factor                                        | 88              | Prospective   | Between 24 and 48 hours and day 7       | CMR, 6.4 months                 | ≥20% increase in LVEDVi        | 15 (16.9%)  | positive (day 7)                        | Ortiz-Perez 2013         |
| Serum soluble ACE2                                   | 227             | Prospective   | day 1, day 7                            | CMR, 6 months                   | ≥20% increase in LVEDV         | 29 (16%)    | positive (d1 and d7), multivariate (d7) | Calderney 2019           |
| soluble AXL                                          | 48              | RCT substudy  | prior to PCI and 24 hours               | CMR, 4 months                   | changes in LVEDVi and LVEDV    | NA          | none                                    | Nilsson 2013             |
| soluble FAS                                          | 33 (AMI)        | Not available | day 1, day 7 and day 14                 | Left ventriculography, 6 months | unavailable                    | NA          | none                                    | Kondo 2009               |
| soluble FAS ligand                                   | 48              | RCT substudy  | prior to PCI and 24 hours               | CMR, 4 months                   | changes in LVEDVi and LVEDV    | NA          | none                                    | Nilsson 2013             |
| Soluble interleukin-1 receptor 2                     | 255             | RCT substudy  | before and immediately after PCI, day 1 | CMR, 4 months                   | change in LVEDVi and LVEDV     | NA          | positive                                | Orrem 2018               |
| Soluble interleukin-1 receptor-like 1 (ST2)          | 109             | Prospective   | 24 hours after reperfusion              | CMR, 6 months                   | change in LVEDVi and LVEDV     | NA          | positive                                | Mihana 2018              |
| Soluble Tumour Necrosis Factor Receptor 2            | 48              | RCT substudy  | prior to PCI and 24 hours               | CMR, 4 months                   | changes in LVEDVi and LVEDV    | NA          | none                                    | Nilsson 2013             |
| Total Antioxidant Capacity                           | 255             | Retrospective | at admission, 24 hours                  | TTE, 6 months                   | ≥20% increase in LVEDV         | 60 (23.5%)  | negative                                | Turkoglu 2016            |
| Total Oxidant Status                                 | 255             | Retrospective | at admission, 24 hours                  | TTE, 6 months                   | ≥20% increase in LVEDV         | 60 (23.5%)  | positive                                | Turkoglu 2016            |
| Vascular endothelial growth factor-1                 | 290 (84% STEMI) | Prospective   | before discharge (average day 4)        | TTE, 6 months                   | increase in LVEDV              | 146 (50%)   | negative, multivariate                  | Devaux 2012              |
| Vascular endothelial growth factor-2                 | 40 (AMI)        | Not available | at admission, day 7, day 14             | Left ventriculography, 3 months | an increase in LVEDVi ≥5 ml/m2 | 15 (37.5%)  | none                                    | Soeki 2002               |
| Vascular endothelial growth factor-2 gene expression | 62              | Prospective   | within 24 hours                         | TTE, 1 month                    | ≥20% increase in LVEDV         | 16 (26%)    | none                                    | Abdel Hamid 2016         |
| vonWillebrand factor                                 | 62              | Prospective   | within 24 hours                         | TTE, 1 month                    | ≥20% increase in LVEDV         | 16 (26%)    | none                                    | Abdel Hamid 2016         |
| β1-adrenoreceptor autoantibody                       | 478             | Not available | overnight after admission               | TTE, 12 months                  | ≥15% increase in LVEDV         | 226 (47.3%) | positive, multivariate                  | Fan 2017                 |

## REFERENCES

- Abate E, Hoogslag GE, Leong DP, Bertini M, Antoni ML, Nucifora G, Joyce E, Holman ER, Siebelink HM, Schalij MJ, Bax JJ, Delgado V, Ajmone Marsan N. Association between multilayer left ventricular rotational mechanics and the development of left ventricular remodeling after acute myocardial infarction. *J Am Soc Echocardiogr.* 2014;27(3):239-48. <https://doi.org/10.1016/j.echo.2013.12.009>
- Abdel Hamid M, Bakhoun SW, Sharaf Y, Sabry D, El-Gengehe AT, Abdel-Latif A. Circulating Endothelial Cells and Endothelial Function Predict Major Adverse Cardiac Events and Early Adverse Left Ventricular Remodeling in Patients With ST-Segment Elevation Myocardial Infarction. *J Interv Cardiol.* 2016;29(1):89-98. <https://doi.org/10.1111/joic.12269>
- Acar B, Ozeke O, Unal S, Karakurt M, Kara M, Kirbas O, Sen F, Korkmaz A, Aras D, Aydogdu S. Change in left ventricular systolic function in patients with ST elevation myocardial infarction: Evidence for smoker's paradox or pseudo-paradox? *Indian Heart J.* 2016;68(6):816-820. <https://doi.org/10.1016/j.ihj.2016.04.001>
- Ahn KT, Song YB, Choe YH, Yang JH, Hahn JY, Choi JH, Choi SH, Chang SA, Lee SC, Lee SH, Oh JK, Gwon HC. Impact of transmural necrosis on left ventricular remodeling and clinical outcomes in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Int J Cardiovasc Imaging.* 2013;29(4):835-42
- Andrejic OM, Vucic RM, Pavlovic M, McClements L, Stokanovic D, Jevtovic-Stoimenov T, Nikolic VN. Association between Galectin-3 levels within central and peripheral venous blood, and adverse left ventricular remodelling after first acute myocardial infarction. *Sci Rep.* 2019;9(1):13145. <https://doi.org/10.1038/s41598-019-49511-4>
- Aoki S, Nakagomi A, Asai K, Takano H, Yasutake M, Seino Y, Mizuno K. Elevated peripheral blood mononuclear cell count is an independent predictor of left ventricular remodeling in patients with acute myocardial infarction. *J Cardiol.* 2011;57(2):202-7. <https://doi.org/10.1016/j.jcc.2010.10.003>
- Araszkiewicz A, Janus M, Prech M, Grygier M, Pyda M, Ołasińska-Wisniewska A, Araszkiewicz A, Mularek-Kubzdela T, Lesiak M, Grajek S. Relations of diabetes mellitus, microvascular reperfusion and left ventricular remodelling in patients with acute myocardial infarction treated with primary coronary intervention. *Kardiol Pol.* 2014;72(1):20-6. <https://doi.org/10.5603/KP.a2013.0185>
- Awadalla H, Saleh MA, Abdel Kader M, Mansour A. Left ventricular torsion assessed by two-dimensional echocardiography speckle tracking as a predictor of left ventricular remodeling and short-term outcome following primary percutaneous coronary intervention for acute myocardial infarction: A single-center experience. *Echocardiography.* 2017;34(8):1159-1169. <https://doi.org/10.1111/echo.13611>
- Barberato SH, Souza AM, Costantini CO, Costantini CR. Non invasive assessment of left ventricular filling pressure and remodeling after acute myocardial infarction. *Arq Bras Cardiol.* 2013;100(6):531-7. <https://doi.org/10.5935/abc.20130092>
- Bastawy I, Ismail M, Hanna HF, El Kilany W. Speckle tracking imaging as a predictor of left ventricular remodeling 6 months after first anterior ST elevation myocardial infarction in patients managed by primary percutaneous coronary intervention. *Egypt Heart J.* 2018;70(4):343-352. <https://doi.org/10.1016/j.ehj.2018.06.006>
- Bauters C, Ennezat PV, Tricot O, Lauwerier B, Lallemand R, Saadouni H, Quandalle P, Jaboureck O, Lamblin N, Le Tourneau T; REVE Investigators. Stress hyperglycaemia is an independent predictor of left ventricular remodelling after first anterior myocardial infarction in non-diabetic patients. *Eur Heart J.* 2007;28(5):546-52. <https://doi.org/10.1093/eurheartj/ehl546>
- Bauters C, Kumarswamy R, Holzmann A, Bretthauer J, Anker SD, Pinet F, Thum T. Circulating miR-133a and miR-423-5p fail as biomarkers for left ventricular remodeling after myocardial infarction. *Int J Cardiol.* 2013;168(3):1837-40. <https://doi.org/10.1016/j.ijcard.2012.12.074>
- Bochenek T, Wita K, Tabor Z, Grabka M, Krzych Ł, Wróbel W, Berger-Kucza A, Elżbieciak M, Doruchowska A, Gluza MT. Value of speckle-tracking echocardiography for prediction of left ventricular remodeling in patients with ST-elevation myocardial infarction treated by primary percutaneous intervention. *J Am Soc Echocardiogr.* 2011;24(12):1342-8. <https://doi.org/10.1016/j.echo.2011.09.003>
- Bonios MJ, Kaladaridou A, Tasoulis A, Papadopoulou E, Pamboukas C, Ntalianis A, Kanakakis J, Terrovitis JV, Toumanidis ST. Value of apical circumferential strain in the early post-myocardial infarction period for prediction of left ventricular remodeling. *Hellenic J Cardiol.* 2014;55(4):305-12.
- Buono F, Spinelli L, Giallauria F, Assante di Panzillo E, Di Marino S, Ferrara F, Vigorito C, Trimarco B, Morisco C. Usefulness of satisfactory control of low-density lipoprotein cholesterol to predict left ventricular remodeling after a first ST-elevation myocardial infarction successfully reperfused. *Am J Cardiol.* 2011;107(12):1772-8. <https://doi.org/10.1016/j.amjcard.2011.01.066>

- Caldentey G, García De Frutos P, Cristóbal H, Garabito M, Berrueto A, Bosch X, San Antonio R, Flores-Umanzor E, Perea RJ, De Caralt TM, Rodríguez J, Ortiz-Pérez JT. Serum levels of Growth Arrest-Specific 6 protein and soluble AXL in patients with ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2019;8(8):708-716
- Carrabba N, Parodi G, Valenti R, Migliorini A, Bellandi B, Antoniucci D. Prognostic value of reverse left ventricular remodeling after primary angioplasty for STEMI. *Atherosclerosis*. 2012;222(1):123-8. <https://doi.org/10.1016/j.atherosclerosis.2012.02.028>
- Cerisano G, Buonamici P, Gori AM, Valenti R, Sciagrà R, Giusti B, Sereni A, Raspanti S, Colonna P, Gensini GF, Abbate R, Schulz R, Antoniucci D. Matrix metalloproteinases and their tissue inhibitor after reperfused ST-elevation myocardial infarction treated with doxycycline. Insights from the TIPTOP trial. *Int J Cardiol*. 2015;197:147-53. <https://doi.org/10.1016/j.ijcard.2015.06.024>
- Cha MJ, Lee JH, Jung HN, Kim Y, Choe YH, Kim SM. Cardiac magnetic resonance-tissue tracking for the early prediction of adverse left ventricular remodeling after ST-segment elevation myocardial infarction. *Int J Cardiovasc Imaging*. 2019;35(11):2095-2102 <https://doi.org/10.1007/s10554-019-01659-w>
- Choe JC, Cha KS, Yun EY, Ahn J, Park JS, Lee HW, Oh JH, Kim JS, Choi JH, Park YH, Lee HC, Kim JH, Chun KJ, Hong TJ, Ahn Y, Jeong MH, Chae SC, Kim YJ; Korea Acute Myocardial Infarction Registry Investigators. Reverse Left Ventricular Remodelling in ST-Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention: Incidence, Predictors, and Impact on Outcome. *Heart Lung Circ*. 2018;27(2):154-164. <https://doi.org/10.1016/j.hlc.2017.02.020>
- Choi H, Yoo BS, Doh JH, Yoo HJ, Ahn MS, Kim JY, Lee SH, Yoon J. The optimal time of B-type natriuretic peptide sampling associated with post-myocardial infarction remodelling after primary percutaneous coronary intervention. *Cardiovasc J Afr*. 2013;24(5):165-70. <https://doi.org/10.5830/CVJA-2013-024>
- Chu AA, Wu TT, Zhang L, Zhang Z. The prognostic value of left atrial and left ventricular strain in patients after ST-segment-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Cardiol J*. 2020 Feb 10. <https://doi.org/10.5603/CJ.a2020.0010>
- Cogni AL, Farah E, Minicucci MF, Azevedo PS, Okoshi K, Matsubara BB, Zanati SG, Paiva SA, Zornoff LA. Waist circumference, but not body mass index, is a predictor of ventricular remodeling after anterior myocardial infarction. *Nutrition*. 2013;29(1):122-6. <https://doi.org/10.1016/j.nut.2012.04.020>
- de Gonzalo-Calvo D, Cediel G, Bär C, Núñez J, Revuelta-Lopez E, Gavara J, Ríos-Navarro C, Llorente-Cortes V, Bodí V, Thum T, Bayes-Genis A. Circulating miR-1254 predicts ventricular remodeling in patients with ST-Segment-Elevation Myocardial Infarction: A cardiovascular magnetic resonance study. *Sci Rep*. 2018;8(1):15115. <https://doi.org/10.1038/s41598-018-33491-y>
- Devaux Y, Vausort M, Azuaje F, Vaillant M, Lair ML, Gayat E, Lassus J, Ng LL, Kelly D, Wagner DR, Squire IB. Low levels of vascular endothelial growth factor B predict left ventricular remodeling after acute myocardial infarction. *J Card Fail*. 2012;18(4):330-7. <https://doi.org/10.1016/j.cardfail.2012.01.010>
- Devaux Y, Vausort M, McCann GP, Zangrando J, Kelly D, Razvi N, Zhang L, Ng LL, Wagner DR, Squire IB. MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. *Circ Cardiovasc Genet*. 2013;6(3):290-8. <https://doi.org/10.1161/CIRCGENETICS.113.000077>
- Di Tano G, Caretta G, De Maria R, Parolini M, Bassi L, Testa S, Pirelli S. Galectin-3 predicts left ventricular remodelling after anterior-wall myocardial infarction treated by primary percutaneous coronary intervention. *Heart*. 2017;103(1):71-77. <https://doi.org/10.1136/heartjnl-2016-309673>
- Domínguez-Rodríguez A, Abreu-Gonzalez P, Avanzas P, Laynez-Cerdeña I, Kaski JC. Neopterin predicts left ventricular remodeling in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Atherosclerosis*. 2010;211(2):574-8. <https://doi.org/10.1016/j.atherosclerosis.2010.04.017>
- Domínguez-Rodríguez A, Abreu-Gonzalez P, Avanzas P. Relation of growth-differentiation factor 15 to left ventricular remodeling in ST-segment elevation myocardial infarction. *Am J Cardiol*. 2011;108(7):955-8. <https://doi.org/10.1016/j.amjcard.2011.05.028>
- Domínguez-Rodríguez A, Abreu-Gonzalez P, Arroyo-Ucar E, Reiter RJ. Decreased level of melatonin in serum predicts left ventricular remodelling after acute myocardial infarction. *J Pineal Res*. 2012;53(3):319-23. <https://doi.org/10.1111/j.1600-079X.2012.01001.x>
- Elżbieciak M, Wita K, Grabka M, Chmurawa J, Doruchowska A, Turski M, Filipecki A, Wybraniec M, Mizia-Stec K. Effect of postconditioning on infarction size, adverse left ventricular remodeling, and improvement in left ventricular systolic function in patients with first anterior ST-segment elevation myocardial infarction. *Pol Arch Med Wewn*. 2013;123(6):268-76. <https://doi.org/10.20452/pamw.1766>
- Erkol A, Oduncu V, Pala S, Kızılırmak F, Kılıçgedik A, Yılmaz F, Güler A, Karabay CY, Kirma C. Plasma osteoprotegerin level on admission is associated with no-reflow phenomenon after primary

- angioplasty and subsequent left ventricular remodeling in patients with acute ST-segment elevation myocardial infarction. *Atherosclerosis*. 2012;221(1):254-9. <https://doi.org/10.1016/j.atherosclerosis.2011.12.031>
- Fabregat-Andrés Ó, Ridocci-Soriano F, Estornell-Erill J, Corbí-Pascual M, Valle-Muñoz A, Berenguer-Jofresa A, Barrabés JA, Mata M, Monsalve M. Blood PGC-1 $\alpha$  Concentration Predicts Myocardial Salvage and Ventricular Remodeling After ST-segment Elevation Acute Myocardial Infarction. *Rev Esp Cardiol (Engl Ed)*. 2015;68(5):408-16. <https://doi.org/10.1016/j.rec.2014.05.020>
  - Fan Y, Chen Y, Wan Z, Zhou D, Ma A. The prognostic value of autoantibodies against  $\beta$ 1-adrenoceptor and cardiac troponin-I for clinical outcomes in STEMI. *J Cardiovasc Med (Hagerstown)*. 2017;18(1):34-41
  - Farah E, Fusco DR, Okumoto PR, Minicucci MF, Azevedo PS, Matsubara BB, Okoshi K, Zanati SG, Paiva SA, Zornoff LA. Impact of ventricular geometric pattern on cardiac remodeling after myocardial infarction. *Arq Bras Cardiol*. 2013;100(6):518-23. <https://doi.org/10.5935/abc.20130104>
  - Feistritzer HJ, Klug G, Reinstadler SJ, Gröber MT, Mair J, Kirchmair R, Henninger B, Franz WM, Metzler B. Fetuin-A is related to infarct size, left ventricular function and remodelling after acute STEMI. *Open Heart*. 2015;2(1):e000244. <https://doi.org/10.1136/openhrt-2015-000244>
  - Fertin M, Hennache B, Hamon M, Ennezat PV, Biaisque F, Elkohen M, Nogue O, Tricot O, Lamblin N, Pinet F, Bauters C. Usefulness of serial assessment of B-type natriuretic peptide, troponin I, and C-reactive protein to predict left ventricular remodeling after acute myocardial infarction (from the REVE-2 study). *Am J Cardiol*. 2010;106(10):1410-6. <https://doi.org/10.1016/j.amjcard.2010.06.071>
  - Fertin M, Lemesle G, Turkieh A, Beseme O, Chwastyniak M, Amouyel P, Bauters C, Pinet F. Serum MMP-8: a novel indicator of left ventricular remodeling and cardiac outcome in patients after acute myocardial infarction. *PLoS One*. 2013;8(8):e71280. <https://doi.org/10.1371/journal.pone.0071280>
  - Frey A, Gassenmaier T, Hofmann U, Schmitt D, Fette G, Marx A, Herterich S, Boivin-Jahns V, Ertl G, Bley T, Frantz S, Jahns R, Störk S. Coagulation factor XIII activity predicts left ventricular remodelling after acute myocardial infarction. *ESC Heart Fail*. 2020;7(5):2354-64. <https://doi.org/10.1002/ehf2.12774>
  - Galeano-Otero I, Del Toro R, Guisado A, Díaz I, Mayoral-González I, Guerrero-Márquez F, Gutiérrez-Carretero E, Casquero-Domínguez S, Díaz-de la Llera L, Barón-Esquivias G, Jiménez-Navarro M, Smani T, Ordóñez-Fernández A. Circulating miR-320a as a Predictive Biomarker for Left Ventricular Remodelling in STEMI Patients Undergoing Primary Percutaneous Coronary Intervention. *J Clin Med*. 2020;9(4):1051. <https://doi.org/10.3390/jcm9041051>
  - Ganame J, Messalli G, Masci PG, Dymarkowski S, Abbasi K, Van de Werf F, Janssens S, Bogaert J. Time course of infarct healing and left ventricular remodelling in patients with reperfused ST segment elevation myocardial infarction using comprehensive magnetic resonance imaging. *Eur Radiol*. 2011;21(4):693-701. <https://doi.org/10.1007/s00330-010-1963-8>
  - García G, Chao de la Barca JM, Mirebeau-Prunier D, Reynier P, Furber A, Prunier F, Bière L. Metabolomic Approach in STEMI-Patients Undergoing Left Ventricular Remodeling. *Int J Mol Sci*. 2019;20(2):289. <https://doi.org/10.3390/ijms20020289>
  - García-Alvarez A, Sitges M, Delgado V, Ortiz J, Vidal B, Poyatos S, de Caralt TM, Heras M, Bosch X, Azqueta M, Pare C, Brugada J. Relation of plasma brain natriuretic peptide levels on admission for ST-elevation myocardial infarction to left ventricular end-diastolic volume six months later measured by both echocardiography and cardiac magnetic resonance. *Am J Cardiol*. 2009;104(7):878-82. <https://doi.org/10.1016/j.amjcard.2009.05.025>
  - Gohbara M, Iwahashi N, Kataoka S, Hayakawa Y, Sakamaki K, Akiyama E, Maejima N, Tsukahara K, Hibi K, Kosuge M, Ebina T, Umemura S, Kimura K. Glycemic Variability Determined by Continuous Glucose Monitoring System Predicts Left Ventricular Remodeling in Patients With a First ST-Segment Elevation Myocardial Infarction. *Circ J*. 2015;79(5):1092-9. <https://doi.org/10.1253/circj.CJ-14-1226>
  - Grabka M, Kocierz-Woźnowska M, Wybraniec M, Turski M, Wita M, Wita K, Mizia-Stec K. Left ventricular reverse remodeling in patients with anterior wall ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention. *Postepy Kardiol Interwencyjne*. 2018;14(4):373-382. <https://doi.org/10.5114/aic.2018.79867>
  - Grabmaier U, Clauss S, Gross L, Klier I, Franz WM, Steinbeck G, Wakili R, Theiss HD, Brenner C. Diagnostic and prognostic value of miR-1 and miR-29b on adverse ventricular remodeling after acute myocardial infarction - The SITAGRAMI-miR analysis. *Int J Cardiol*. 2017;244:30-36. <https://doi.org/10.1016/j.ijcard.2017.06.054>
  - Gravning J, Ørn S, Kaasbøll OJ, Martinov VN, Manhenke C, Dickstein K, Edvardsen T, Attramadal H, Ahmed MS. Myocardial connective tissue growth factor (CCN2/CTGF) attenuates left ventricular remodeling after myocardial infarction. *PLoS One*. 2012;7(12):e52120. <https://doi.org/10.1371/journal.pone.0052120>

- Hallén J, Jensen JK, Fagerland MW, Jaffe AS, Atar D. Cardiac troponin I for the prediction of functional recovery and left ventricular remodelling following primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Heart*. 2010;96(23):1892-7. <https://doi.org/10.1136/hrt.2009.190819>
- Hatasa M, Tanaka T, Minatoguchi S, Yamada Y, Kanamori H, Kawasaki M, Nishigaki K, Esaka Y, Uno B, Minatoguchi S. Increased Plasma Adenosine Concentration in the Subacute Phase May Contribute to Attenuation of Left Ventricular Dilation in the Chronic Phase in Patients With Acute Myocardial Infarction. *Circ J*. 2019;83(4):783-792. <https://doi.org/10.1253/circj.CJ-18-1107>
- Helseth R, Shetelig C, Andersen GØ, Langseth MS, Limalanathan S, Opstad TB, Arnesen H, Hoffmann P, Eritsland J, Seljeflot I. Neutrophil Extracellular Trap Components Associate with Infarct Size, Ventricular Function, and Clinical Outcome in STEMI. *Mediators Inflamm*. 2019;2019:7816491. <https://doi.org/10.1155/2019/7816491>
- Hole T, Hall C, Skaerpe T. N-terminal proatrial natriuretic peptide predicts two-year remodelling in patients with acute transmural myocardial infarction. *Eur Heart J*. 2004;25(5):416-23. <https://doi.org/10.1016/j.ehj.2003.10.036>
- Hsiao JF, Chung CM, Chu CM, Lin YS, Pan KL, Chang ST, Hsu JT. Two-Dimensional Speckle Tracking Echocardiography Predict Left Ventricular Remodeling after Acute Myocardial Infarction in Patients with Preserved Ejection Fraction. *PLoS One*. 2016;11(12):e0168109. <https://doi.org/10.1371/journal.pone.0168109>
- Hsu JT, Chung CM, Chu CM, Lin YS, Pan KL, Chang JJ, Wang PC, Chang ST, Yang TY, Jang SJ, Yang TH, Hsiao JF. Predictors of Left Ventricle Remodeling: Combined Plasma B-type Natriuretic Peptide Decreasing Ratio and Peak Creatine Kinase-MB. *Int J Med Sci*. 2017;14(1):75-85. <https://doi.org/10.7150/ijms.17145>
- Husser O, Monmeneu JV, Sanchis J, Nunez J, Lopez-Lereu MP, Bonanad C, Chaustre F, Gomez C, Bosch MJ, Hinarejos R, Chorro FJ, Riegger GA, Llacer A, Bodi V. Cardiovascular magnetic resonance-derived intramyocardial hemorrhage after STEMI: Influence on long-term prognosis, adverse left ventricular remodeling and relationship with microvascular obstruction. *Int J Cardiol*. 2013;167(5):2047-54. <https://doi.org/10.1016/j.ijcard.2012.05.055>
- Joyce E, Hoogslag GE, Leong DP, Fox K, Schali J, Marsan NA, Bax JJ, Delgado V. Association between discharge heart rate and left ventricular adverse remodelling in ST segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *Heart*. 2013;99(8):556-61. <https://doi.org/10.1136/heartjnl-2012-303406>
- Karuzas A, Rumbinaite E, Verikas D, Ptasinikas T, Muckiene G, Kazakauskaitė E, Zabiela V, Jurkevicius R, Vaskelyte JJ, Zaliunas R, Zaliaduonyte-Peksiene D. Accuracy of three-dimensional systolic dyssynchrony and sphericity indexes for identifying early left ventricular remodeling after acute myocardial infarction. *Anatol J Cardiol*. 2019;22(1):13-20. <https://doi.org/10.14744/AnatolJCardiol.2019.02844>
- Kenar Tiryakioglu S, Ozkan H, Ari H, Yalin K, Coskun S, Tiryakioglu O. Assessment of the Utility of the Septal E/(E' × S') Ratio and Tissue Doppler Index in Predicting Left Ventricular Remodeling after Acute Myocardial Infarction. *Biomed Res Int*. 2016;2016:4954731. <https://doi.org/10.1155/2016/4954731>
- Khurelsukh K, Kim YH, Seon HJ, Song JH, Park SY, Moon SM, Kim SH, Sim DS, Ahn Y. Non-contrast cardiac CT immediately after percutaneous coronary intervention: does it predict the risk of left ventricular remodeling in patients with ST-elevation myocardial infarction? *Int J Cardiovasc Imaging*. 2016;32 Suppl 1:147-54. <https://doi.org/10.1007/s10554-016-0900-6>
- Kim EK, Song YB, Chang SA, Park SJ, Hahn JY, Choi SH, Choi JH, Gwon HC, Park SW, Choe YH, Ahn J, Carriere K, Lee SC. Is cardiac magnetic resonance necessary for prediction of left ventricular remodeling in patients with reperfused ST-segment elevation myocardial infarction? *Int J Cardiovasc Imaging*. 2017;33(12):2003-2012. <https://doi.org/10.1007/s10554-017-1206-z>
- Kondo H, Hojo Y, Tsuru R, Nishimura Y, Shimizu H, Takahashi N, Hirose M, Ikemoto T, Ohya K, Katsuki T, Yashiro T, Shimada K. Elevation of plasma granzyme B levels after acute myocardial infarction. *Circ J*. 2009;73(3):503-7. <https://doi.org/10.1253/circj.cj-08-0668>
- Lacalzada J, de la Rosa A, Izquierdo MM, Jiménez JJ, Iribarren JL, García-González MJ, López BM, Duque MA, Barragán A, Hernández C, Carrillo-Pérez M, Laynez I. Left ventricular global longitudinal systolic strain predicts adverse remodeling and subsequent cardiac events in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. *Int J Cardiovasc Imaging*. 2015;31(3):575-84. <https://doi.org/10.1007/s10554-015-0593-2>
- Legallois D, Macquaire C, Hodzic A, Allouche S, El Khouakhi I, Manrique A, Milliez P, Saloux E, Beygui F. Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction. *BMC Cardiovasc Disord*. 2020;20(1):316. <https://doi.org/10.1186/s12872-020-01578-y>

- Lin JF, Wu S, Hsu SY, Yeh KH, Chou HH, Cheng ST, Wu TY, Hsu WT, Yang CC, Ko YL. Growth-differentiation factor-15 and major cardiac events. *Am J Med Sci.* 2014;347(4):305-11. <https://doi.org/10.1097/MAJ.0b013e318291cd4e>
- Lin JF, Hsu SY, Wu S, Teng MS, Chou HH, Cheng ST, Wu TY, Ko YL. QT interval Independently Predicts Mortality and Heart Failure in Patients with ST-Elevation Myocardial Infarction. *Int J Med Sci.* 2015;12(12):968-73. <https://doi.org/10.7150/ijms.13121>
- Liu X, Dong Y, Chen S, Zhang G, Zhang M, Gong Y, Li X. Circulating MicroRNA-146a and MicroRNA-21 Predict Left Ventricular Remodeling after ST-Elevation Myocardial Infarction. *Cardiology.* 2015;132(4):233-41. <https://doi.org/10.1159/000437090>
- Liu PY, Chen CL, Yu MC, Ko YL, Hsu SY, Chou HH, Yeh KH, Duan DM, Chen MH, Lin JF. Doses of renin-angiotensin system inhibitors but not beta-blockers predict outcome after ST-elevation myocardial infarction. *Acta Clin Belg.* 2019;74(5):334-341. <https://doi.org/10.1080/17843286.2018.1528708>
- Lombardo A, Niccoli G, Natale L, Bernardini A, Cosentino N, Bonomo L, Crea F. Impact of microvascular obstruction and infarct size on left ventricular remodeling in reperfused myocardial infarction: a contrast-enhanced cardiac magnetic resonance imaging study. *Int J Cardiovasc Imaging.* 2012;28(4):835-42. <https://doi.org/10.1007/s10554-011-9901-7>
- Lustosa RP, van der Bijl P, El Mahdiui M, Montero-Cabezas JM, Kostyukevich MV, Ajmone Marsan N, Bax JJ, Delgado V. Noninvasive Myocardial Work Indices 3 Months after ST-Segment Elevation Myocardial Infarction: Prevalence and Characteristics of Patients with Postinfarction Cardiac Remodeling. *J Am Soc Echocardiogr.* 2020;33(10):1172-1179. <https://doi.org/10.1016/j.echo.2020.05.001>
- Lv P, Zhou M, He J, Meng W, Ma X, Dong S, Meng X, Zhao X, Wang X, He F. Circulating miR-208b and miR-34a are associated with left ventricular remodeling after acute myocardial infarction. *Int J Mol Sci.* 2014;15(4):5774-88. <https://doi.org/10.3390/ijms15045774>
- Manhenke C, Ueland T, Jugdutt BI, Godang K, Aukrust P, Dickstein K, Ørn S. The relationship between markers of extracellular cardiac matrix turnover: infarct healing and left ventricular remodelling following primary PCI in patients with first-time STEMI. *Eur Heart J.* 2014;35(6):395-402. <https://doi.org/10.1093/eurheartj/ehf482>
- Manrique A, Lemarchand P, Delasalle B, Lairez O, Sportouch-Duckan C, Lamirault G, Le Corvoisier P, Neuder Y, Richardson M, Lebon A, Roncalli J, Piot C, Trochu JN, Teiger E, Hossein-Foucher C, Le Tourneau T. Predictors of ventricular remodelling in patients with reperfused acute myocardial infarction and left ventricular dysfunction candidates for bone marrow cell therapy: insights from the BONAMI trial. *Eur J Nucl Med Mol Imaging.* 2016;43(4):740-8. <https://doi.org/10.1007/s00259-015-3279-z>
- Mather AN, Fairbairn TA, Artis NJ, Greenwood JP, Plein S. Relationship of cardiac biomarkers and reversible and irreversible myocardial injury following acute myocardial infarction as determined by cardiovascular magnetic resonance. *Int J Cardiol.* 2013;166(2):458-64. <https://doi.org/10.1016/j.ijcard.2011.11.004>
- Meng L, Wang J, Ding WH, Han P, Yang Y, Qi LT, Zhang BW. Plasma catestatin level in patients with acute myocardial infarction and its correlation with ventricular remodelling. *Postgrad Med J.* 2013;89(1050):193-6. <https://doi.org/10.1136/postgradmedj-2012-131060>
- Miñana G, Núñez J, Bayés-Genís A, Revuelta-López E, Ríos-Navarro C, Núñez E, Chorro FJ, López-Lereu MP, Monmeneu JV, Lupón J, Bodí V. ST2 and left ventricular remodeling after ST-segment elevation myocardial infarction: A cardiac magnetic resonance study. *Int J Cardiol.* 2018;270:336-342. <https://doi.org/10.1016/j.ijcard.2018.06.073>
- Miranda B, Barrabés JA, Figueras J, Pineda V, Rodríguez-Palomares J, Lidón RM, Sambola A, Bañeras J, Otaegui I, García-Dorado D. Plasma bilirubin values on admission and ventricular remodeling after a first anterior ST-segment elevation acute myocardial infarction. *Ann Med.* 2016;48(1-2):1-9. <https://doi.org/10.3109/07853890.2015.1112027>
- Na HM, Cho GY, Lee JM, Cha MJ, Yoon YE, Lee SP, Kim HK, Kim YJ, Sohn DW. Echocardiographic Predictors for Left Ventricular Remodeling after Acute ST Elevation Myocardial Infarction with Low Risk Group: Speckle Tracking Analysis. *J Cardiovasc Ultrasound.* 2016;24(2):128-34. <https://doi.org/10.4250/jcu.2016.24.2.128>
- Nilsson L, Szymanski A, Swahn E, Jonasson L. Soluble TNF receptors are associated with infarct size and ventricular dysfunction in ST-elevation myocardial infarction. *PLoS One.* 2013;8(2):e55477. <https://doi.org/10.1371/journal.pone.0055477>
- Nucifora G, Marsan NA, Bertini M, Delgado V, Siebelink HM, van Werkhoven JM, Scholte AJ, Schalij MJ, van der Wall EE, Holman ER, Bax JJ. Reduced left ventricular torsion early after myocardial infarction is related to left ventricular remodeling. *Circ Cardiovasc Imaging.* 2010;3(4):433-42. <https://doi.org/10.1161/CIRCIMAGING.109.926196>

- O'Regan DP, Shi W, Ariff B, Baksi AJ, Durighel G, Rueckert D, Cook SA. Remodeling after acute myocardial infarction: mapping ventricular dilatation using three dimensional CMR image registration. *J Cardiovasc Magn Reson*. 2012;14(1):41. <https://doi.org/10.1186/1532-429X-14-41>
- Obata JE, Horikoshi T, Nakamura T, Kugiyama K. Sustained endothelial dysfunction in the infarct-related coronary artery is associated with left ventricular adverse remodeling in survivors of ST-segment elevation myocardial infarction. *J Cardiol*. 2020;75(3):261-269. <https://doi.org/10.1016/j.jjcc.2019.08.001>
- Orrem HL, Shetelig C, Ueland T, Limalanathan S, Nilsson PH, Husebye T, Aukrust P, Seljeflot I, Hoffmann P, Eritsland J, Mollnes TE, Andersen GØ, Yndestad A. Soluble IL-1 receptor 2 is associated with left ventricular remodelling in patients with ST-elevation myocardial infarction. *Int J Cardiol*. 2018;268:187-192. <https://doi.org/10.1016/j.ijcard.2018.05.032>
- Ortiz-Pérez JT, Riera M, Bosch X, De Caralt TM, Perea RJ, Pascual J, Soler MJ. Role of circulating angiotensin converting enzyme 2 in left ventricular remodeling following myocardial infarction: a prospective controlled study. *PLoS One*. 2013;8(4):e61695. <https://doi.org/10.1371/journal.pone.0061695>
- Piestrzeniewicz K, Luczak K, Maciejewski M, Drozd J. Low adiponectin blood concentration predicts left ventricular remodeling after ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *Cardiol J*. 2010;17(1):49-56
- Porto I, De Maria GL, Leone AM, Dato I, D'Amario D, Burzotta F, Niccoli G, Trani C, Biasucci LM, Bolognese L, Crea F. Endothelial progenitor cells, microvascular obstruction, and left ventricular remodeling in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol*. 2013;112(6):782-91. <https://doi.org/10.1016/j.amjcard.2013.04.056>
- Radovan J, Vaclav P, Petr W, Jan C, Michal A, Richard P, Martina P. Changes of collagen metabolism predict the left ventricular remodeling after myocardial infarction. *Mol Cell Biochem*. 2006;293(1-2):71-8. <https://doi.org/10.1007/s11010-006-2955-5>
- Reindl M, Reinstadler SJ, Feistritzer HJ, Tiller C, Mayr A, Klug G, Metzler B. Heart rate and left ventricular adverse remodelling after ST-elevation myocardial infarction. *Int J Cardiol*. 2016;219:339-44. <https://doi.org/10.1016/j.ijcard.2016.06.046>
- Reindl M, Reinstadler SJ, Feistritzer HJ, Mueller L, Koch C, Mayr A, Theurl M, Kirchmair R, Klug G, Metzler B. Fibroblast growth factor 23 as novel biomarker for early risk stratification after ST-elevation myocardial infarction. *Heart*. 2017;103(11):856-862. <https://doi.org/10.1136/heartjnl-2016-310520>
- Reindl M, Feistritzer HJ, Reinstadler SJ, Mueller L, Tiller C, Brenner C, Mayr A, Henninger B, Mair J, Klug G, Metzler B. Thyroid-stimulating hormone and adverse left ventricular remodeling following ST-segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2019;8(8):717-726. <https://doi.org/10.1177/2048872618770600>
- Reinstadler SJ, Klug G, Feistritzer HJ, Mayr A, Harrasser B, Mair J, Bader K, Streil K, Hammerer-Lercher A, Esterhammer R, Metzler B. Association of copeptin with myocardial infarct size and myocardial function after ST segment elevation myocardial infarction. *Heart*. 2013;99(20):1525-9. <https://doi.org/10.1136/heartjnl-2013-303975>
- Reinstadler SJ, Feistritzer HJ, Reindl M, Klug G, Mayr A, Mair J, Jaschke W, Metzler B. Combined biomarker testing for the prediction of left ventricular remodelling in ST-elevation myocardial infarction. *Open Heart*. 2016;3(2):e000485. <https://doi.org/10.1136/openhrt-2016-000485>
- Sato A, Aonuma K, Imanaka-Yoshida K, Yoshida T, Isobe M, Kawase D, Kinoshita N, Yazaki Y, Hiroe M. Serum tenascin-C might be a novel predictor of left ventricular remodeling and prognosis after acute myocardial infarction. *J Am Coll Cardiol*. 2006;47(11):2319-25. <https://doi.org/10.1016/j.jacc.2006.03.033>
- Schoos MM, Munthe-Fog L, Skjoedt MO, Ripa RS, Lønborg J, Kastrup J, Kelbæk H, Clemmensen P, Garred P. Association between lectin complement pathway initiators, C-reactive protein and left ventricular remodeling in myocardial infarction-a magnetic resonance study. *Mol Immunol*. 2013;54(3-4):408-14. <https://doi.org/10.1016/j.molimm.2013.01.008>
- Shetelig C, Limalanathan S, Hoffmann P, Seljeflot I, Gran JM, Eritsland J, Andersen GØ. Association of IL-8 With Infarct Size and Clinical Outcomes in Patients With STEMI. *J Am Coll Cardiol*. 2018;72(2):187-198. <https://doi.org/10.1016/j.jacc.2018.04.053>
- Soeki T, Tamura Y, Shinohara H, Sakabe K, Onose Y, Fukuda N. Serum hepatocyte growth factor predicts ventricular remodeling following myocardial infarction. *Circ J*. 2002;66(11):1003-7. <https://doi.org/10.1253/circj.66.1003>

- Spinelli L, Morisco C, Assante di Panzillo E, Izzo R, Trimarco B. Reverse left ventricular remodeling after acute myocardial infarction: the prognostic impact of left ventricular global torsion. *Int J Cardiovasc Imaging*. 2013;29(4):787-95. <https://doi.org/10.1007/s10554-012-0159-5>
- Spinelli L, Stabile E, Giugliano G, Morisco C, Giudice CA, Imbriaco M, Santoro M, Esposito G, Trimarco B. Intramyocardial dissecting hematoma in anterior wall ST elevation myocardial infarction: impact on left ventricular remodeling and prognosis. *Int J Cardiovasc Imaging*. 2018;34(2):201-210. <https://doi.org/10.1007/s10554-017-1221-0>
- Sugano A, Seo Y, Ishizu T, Watabe H, Yamamoto M, Machino-Ohtsuka T, Takaiwa Y, Kakefuda Y, Aihara H, Fumikura Y, Nishina H, Noguchi Y, Aonuma K. Value of 3-Dimensional Speckle Tracking Echocardiography in the Prediction of Microvascular Obstruction and Left Ventricular Remodeling in Patients With ST-Elevation Myocardial Infarction. *Circ J*. 2017;81(3):353-360. <https://doi.org/10.1253/circj.CJ-16-0944>
- Sumiyoshi A, Fujii K, Fukunaga M, Shibuya M, Imanaka T, Kawai K, Miki K, Tamaru H, Horimatsu T, Saita T, Nishimura M, Masuyama T, Ishihara M. Impact of thermodilution-derived coronary blood flow patterns after percutaneous coronary intervention on mid-term left ventricular remodeling in patients with ST elevation myocardial infarction. *Heart Vessels*. 2017;32(1):1-7. <https://doi.org/10.1007/s00380-016-0831-0>
- Swiatkiewicz I, Kozinski M, Magielski P, Fabiszak T, Sukiennik A, Navarese EP, Odrowaz-Sypniewska G, Kubica J. Value of C-reactive protein in predicting left ventricular remodelling in patients with a first ST-segment elevation myocardial infarction. *Mediators Inflamm*. 2012;2012:250867. <https://doi.org/10.1155/2012/250867>
- Symons R, Masci PG, Francone M, Claus P, Barison A, Carbone I, Agati L, Galea N, Janssens S, Bogaert J. Impact of active smoking on myocardial infarction severity in reperfused ST-segment elevation myocardial infarction patients: the smoker's paradox revisited. *Eur Heart J*. 2016;37(36):2756-2764. <https://doi.org/10.1093/eurheartj/ehv738>
- Turan B, Yilmaz F, Karaahmet T, Tigen K, Mutlu B, Basaran Y. Role of left ventricular dyssynchrony in predicting remodeling after ST elevation myocardial infarction. *Echocardiography*. 2012;29(2):165-72. <https://doi.org/10.1111/j.1540-8175.2011.01574.x>
- Türkoğlu C, Gür M, Şeker T, Selek Ş, Koçyiğit A. The predictive value of M30 and oxidative stress for left ventricular remodeling in patients with anterior ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *Coron Artery Dis*. 2016;27(8):690-695. <https://doi.org/10.1097/MCA.0000000000000416>
- Urbano-Moral JA, Lopez-Haldon JE, Fernandez M, Mancha F, Sanchez A, Rodriguez-Puras MJ, Villa M, Lopez-Pardo F, Diaz de la Llera L, Valle JI, Martinez A. Prognostic value of different serum biomarkers for left ventricular remodelling after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. 2012;98(15):1153-9. <https://doi.org/10.1136/heartjnl-2012-301636>
- van der Bijl P, Abou R, Goedemans L, Gersh BJ, Holmes DR Jr, Ajmone Marsan N, Delgado V, Bax JJ. Left Ventricular Post-Infarct Remodeling: Implications for Systolic Function Improvement and Outcomes in the Modern Era. *JACC Heart Fail*. 2020;8(2):131-140. <https://doi.org/10.1016/j.jchf.2019.08.014>
- Watabe H, Sato A, Nishina H, Hoshi T, Sugano A, Kakefuda Y, Takaiwa Y, Aihara H, Fumikura Y, Noguchi Y, Aonuma K. Enhancement patterns detected by multidetector computed tomography are associated with microvascular obstruction and left ventricular remodelling in patients with acute myocardial infarction. *Eur Heart J*. 2016 Feb 21;37(8):684-92. <https://doi.org/10.1093/eurheartj/ehv467>
- Webb CS, Bonnema DD, Ahmed SH, Leonardi AH, McClure CD, Clark LL, Stroud RE, Corn WC, Finklea L, Zile MR, Spinale FG. Specific temporal profile of matrix metalloproteinase release occurs in patients after myocardial infarction: relation to left ventricular remodeling. *Circulation*. 2006;114(10):1020-7. <https://doi.org/10.1161/CIRCULATIONAHA.105.600353>
- Wita K, Filipecki A, Lelek M, Bochenek T, Elżbieciak M, Wróbel W, Berger Kucza A, Tabor Z, Drzewiecki J, Grabka M, Trusz Gluza M. Prediction of left ventricular remodeling in patients with STEMI treated with primary PCI: use of quantitative myocardial contrast echocardiography. *Coron Artery Dis*. 2011;22(3):171-8. <https://doi.org/10.1097/MCA.0b013e328343f8e1>
- Wu W, Li J, Yu C, Gao Y, Fan S, Ye X, Wang Y, Zheng J. Association of serum ADAMTS-7 levels with left ventricular reverse remodeling after ST-elevation myocardial infarction. *Eur J Med Res*. 2018;23(1):15. <https://doi.org/10.1186/s40001-018-0305-1>
- Xu L, Huang X, Ma J, Huang J, Fan Y, Li H, Qiu J, Zhang H, Huang W. Value of three-dimensional strain parameters for predicting left ventricular remodeling after ST-elevation myocardial

- infarction. *Int J Cardiovasc Imaging*. 2017;33(5):663-673. <https://doi.org/10.1007/s10554-016-1053-3>
- Yang CD, Shen Y, Lu L, Ding FH, Yang ZK, Zhang RY, Shen WF, Jin W, Wang XQ. Insulin resistance and dysglycemia are associated with left ventricular remodeling after myocardial infarction in non-diabetic patients. *Cardiovasc Diabetol*. 2019;18(1):100. <https://doi.org/10.1186/s12933-019-0904-3>
  - Yoshitomi Y, Nishikimi T, Kojima S, Kuramochi M, Takishita S, Kangawa K, Matsuo H. Plasma natriuretic peptides as indicators of left ventricular remodeling after myocardial infarction. *Int J Cardiol*. 1998;64(2):153-60. [https://doi.org/10.1016/s0167-5273\(98\)00026-6](https://doi.org/10.1016/s0167-5273(98)00026-6)
  - Zaliaduonyte-Peksiene D, Simonyte S, Lesauskaite V, Vaskelyte J, Gustiene O, Mizariene V, Jurkevicius R, Jariene G, Tamosiunas A, Zaliunas R. Left ventricular remodelling after acute myocardial infarction: impact of clinical, echocardiographic parameters and polymorphism of angiotensinogen gene. *J Renin Angiotensin Aldosterone Syst*. 2014;15(3):286-93. <https://doi.org/10.1177/1470320312471228>

## **Relation entre taux de néprilysine et remodelage ventriculaire gauche**

Cette annexe concerne l'article suivant: **Legallois D**, Macquaire C, Hodzic A, Allouche S, El Khouakhi I, Manrique A, Milliez P, Saloux E, Beygui F. Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction. BMC Cardiovasc Disord. 2020;20(1):316. doi: 10.1186/s12872-020-01578-y

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## Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction

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**Purpose.** Left ventricular remodeling following ST-elevation myocardial infarction (STEMI) is associated with poor outcome. Neprilysin inhibition leads to improved outcome in patients with altered left ventricular ejection fraction (LVEF). We aimed to assess the association between serum levels of neprilysin and left ventricular (LV) volumes, function and remodeling in STEMI patients with successful myocardial reperfusion.

**Methods.** Sixty-eight patients were admitted for STEMI and had both plasma neprilysin measurement at baseline and 3D transthoracic echocardiogram at baseline and at follow-up (7 months). We compared 3 groups: a group with a low-level of plasma neprilysin (<125 pg/mL, i.e. the lower limit of detection of the assay, 38 patients) and the two other groups were defined as being below or above the median value of the remaining samples (15 patients each).

**Results.** Median age was 58.5±12.8 years and 56 (82.4%) were men. Median LVEF was 45.0±8.5%. Baseline characteristics were comparable among groups. At baseline there was a non-significant trend towards lower end-diastolic volume ( $p=0.07$ ) but significantly lower LVEF in the high neprilysin group ( $46.4 \pm 8.3\%$ ,  $47.1 \pm 8.1\%$  and  $39.1 \pm 6.9\%$ ,  $p<0.01$ ).

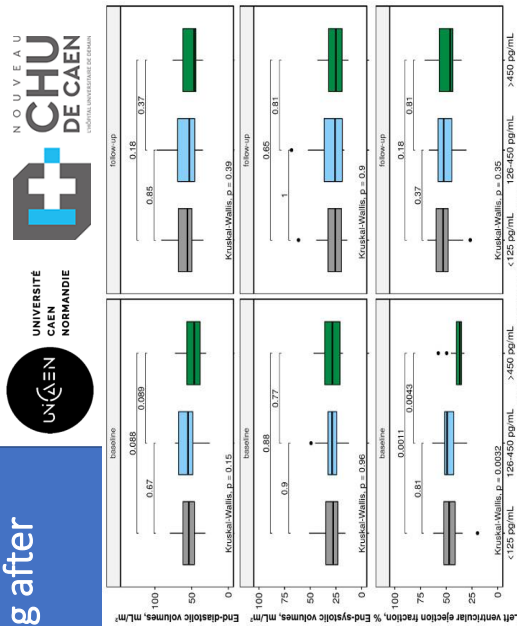


Figure. Relationship between neprilysin levels and LV volumes and function after STEMI

At follow-up, the magnitude of LVEF increase was significantly more important in the high neprilysin group compared to the other groups ( $p=0.022$  for relative change in LVEF and  $6.6 \pm 7.3\%$ ,  $3.6 \pm 9.0\%$  and  $11.3 \pm 8.4\%$ ,  $p=0.031$  for absolute change in LVEF) resulting in similar LVEF levels at follow-up between all groups ( $53.0 \pm 8.9\%$ ,  $50.6 \pm 9.7\%$  and  $50.4 \pm 9.9\%$ ,  $p=0.55$ ).

**Conclusions.** Initial high neprilysin levels may identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up.

|                                  | Overall (n=68)    | Neprilysin level $\leq 125$ pg/mL (n=38) | Neprilysin level 126-450 pg/mL (n=15) | Neprilysin level $>450$ pg/mL (n=15) | Overall p-value | Highest-level vs. Lower groups p-value |
|----------------------------------|-------------------|------------------------------------------|---------------------------------------|--------------------------------------|-----------------|----------------------------------------|
| Baseline EDV, mL/m <sup>2</sup>  | 53.8±13.0         | 55.1±12.4                                | 56.0±13.5                             | 48.3±13.3                            | 0.18            | 0.07                                   |
| Baseline ESV, mL/m <sup>2</sup>  | 28.2 [22.4, 34.7] | 27.8 [23.2, 34.9]                        | 28.8 [24.3, 32.8]                     | 28.5 [21.1, 36.0]                    | 0.97            | 0.82                                   |
| Baseline LVEF, %                 | 45.0±8.5          | 46.4±8.3                                 | 47.1±8.1                              | 39.1±6.9                             | <0.01           | <0.01                                  |
| Follow-up EDV, mL/m <sup>2</sup> | 56.6±15.0         | 57.8±13.6                                | 58.7±19.9                             | 51.6±12.6                            | 0.35            | 0.15                                   |
| Follow-up ESV, mL/m <sup>2</sup> | 25.4 [19.0, 34.8] | 25.8 [19.6, 32.7]                        | 25.9 [18.9, 36.5]                     | 25.1 [19.1, 32.3]                    | 0.91            | 0.66                                   |
| Follow-up LVEF, %                | 51.9±9.2***       | 53.0±8.9***                              | 50.6±9.7                              | 50.4±9.9***                          | 0.55            | 0.49                                   |
| %increase in LVEF                | 17.7±22.0         | 16.0±19.4                                | 9.1±21.5                              | 30.3±24.5                            | 0.022           | 0.01                                   |
| $\Delta$ LVEF, %                 | 7.0±8.3           | 6.6±7.3                                  | 3.6±9.0                               | 11.3±8.4                             | 0.031           | 0.02                                   |

Table. Echocardiographic data according to neprilysin levels at baseline. \*\*\* $p<0.001$  vs. baseline.

# Bibliographie

- [1] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal*. 2017 Aug;39(2):119–177. Available from: <https://doi.org/10.1093/eurheartj/ehx393>.
- [2] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *European Heart Journal*. 2012 Aug;33(20):2551–2567. Available from: <https://doi.org/10.1093/eurheartj/ehs184>.
- [3] Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, Kala P, Mario CD, et al. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. *European Heart Journal*. 2014 Jan;35(29):1957–1970. Available from: <https://doi.org/10.1093/eurheartj/ehs529>.
- [4] Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, et al. Short- and Long-Term Cause of Death in Patients Treated With Primary PCI for STEMI. *Journal of the American College of Cardiology*. 2014 Nov;64(20):2101–2108. Available from: <https://doi.org/10.1016/j.jacc.2014.08.037>.
- [5] Fokkema ML, James SK, Albertsson P, Akerblom A, Calais F, Eriksson P, et al. Population Trends in Percutaneous Coronary Intervention. *Journal of the American College of Cardiology*. 2013 Mar;61(12):1222–1230. Available from: <https://doi.org/10.1016/j.jacc.2013.01.007>.
- [6] Wu E, Ortiz JT, Tejedor P, Lee DC, Bucciarelli-Ducci C, Kansal P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart*. 2008 Jun;94(6):730–736.
- [7] Kelle S, Roes SD, Klein C, Kokocinski T, de Roos A, Fleck E, et al. Prognostic Value of Myocardial Infarct Size and Contractile Reserve Using Magnetic Resonance Imaging. *Journal of the American College of Cardiology*. 2009 Nov;54(19):1770–1777.
- [8] Bauters C, Dubois E, Porouchani S, Saloux E, Fertin M, de Groote P, et al. Long-term prognostic impact of left ventricular remodeling after a first myocardial infarction in modern clinical practice. *PLOS ONE*. 2017 Nov;12(11):e0188884. Available from: <https://doi.org/10.1371/journal.pone.0188884>.
- [9] McKay RG, Pfeffer MA, Pasternak RC, Markis JE, Come PC, Nakao S, et al. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation*. 1986 Oct;74(4):693–702.
- [10] Benjamin MM, Smith RL, Grayburn PA. Ischemic and Functional Mitral Regurgitation in Heart Failure: Natural History and Treatment. *Current Cardiology Reports*. 2014 Jun;16(8).

- [11] Dorn GW. Novel pharmacotherapies to abrogate postinfarction ventricular remodeling. *Nature Reviews Cardiology*. 2009 Apr;6(4):283–291. Available from: <https://doi.org/10.1038/nrcardio.2009.12>.
- [12] Frangogiannis N. The inflammatory response in myocardial infarction. *Cardiovascular Research*. 2002 Jan;53(1):31–47. Available from: [https://doi.org/10.1016/s0008-6363\(01\)00434-5](https://doi.org/10.1016/s0008-6363(01)00434-5).
- [13] Frangogiannis N. The immune system and cardiac repair. *Pharmacological Research*. 2008 Aug;58(2):88–111. Available from: <https://doi.org/10.1016/j.phrs.2008.06.007>.
- [14] Irwin MW, Mak S, Mann DL, Qu R, Penninger JM, Yan A, et al. Tissue Expression and Immunolocalization of Tumor Necrosis Factor- in Postinfarction Dysfunctional Myocardium. *Circulation*. 1999 Mar;99(11):1492–1498. Available from: <https://doi.org/10.1161/01.cir.99.11.1492>.
- [15] Deten A. Cardiac cytokine expression is upregulated in the acute phase after myocardial infarction. Experimental studies in rats. *Cardiovascular Research*. 2002 Aug;55(2):329–340. Available from: [https://doi.org/10.1016/s0008-6363\(02\)00413-3](https://doi.org/10.1016/s0008-6363(02)00413-3).
- [16] Lindsey ML. MMP Induction and Inhibition in Myocardial Infarction. *Heart Failure Reviews*. 2004 Jan;9(1):7–19. Available from: <https://doi.org/10.1023/b:hrev.0000011390.44039.b7>.
- [17] Cleutjens J, Kandala J, Guarda E, Guntaka R, Weber K. Regulation of collagen degradation in the rat myocardium after infarction. *Journal of Molecular and Cellular Cardiology*. 1995 Jun;27(6):1281–1292. Available from: [https://doi.org/10.1016/s0022-2828\(05\)82390-9](https://doi.org/10.1016/s0022-2828(05)82390-9).
- [18] Kain V, Prabhu SD, Halade GV. Inflammation revisited: inflammation versus resolution of inflammation following myocardial infarction. *Basic Research in Cardiology*. 2014 Sep;109(6). Available from: <https://doi.org/10.1007/s00395-014-0444-7>.
- [19] Panizzi P, Swirski FK, Figueiredo JL, Waterman P, Sosnovik DE, Aikawa E, et al. Impaired Infarct Healing in Atherosclerotic Mice With Ly-6Chi Monocytosis. *Journal of the American College of Cardiology*. 2010 Apr;55(15):1629–1638. Available from: <https://doi.org/10.1016/j.jacc.2009.08.089>.
- [20] Frangogiannis NG. Regulation of the Inflammatory Response in Cardiac Repair. *Circulation Research*. 2012 Jan;110(1):159–173. Available from: <https://doi.org/10.1161/circresaha.111.243162>.
- [21] Nahrendorf M, Pittet MJ, Swirski FK. Monocytes: Protagonists of Infarct Inflammation and Repair After Myocardial Infarction. *Circulation*. 2010 Jun;121(22):2437–2445. Available from: <https://doi.org/10.1161/circulationaha.109.916346>.
- [22] Frangogiannis N. Myofibroblasts in reperfused myocardial infarcts express the embryonic form of smooth muscle myosin heavy chain (SMemb). *Cardiovascular Research*. 2000 Oct;48(1):89–100. Available from: [https://doi.org/10.1016/s0008-6363\(00\)00158-9](https://doi.org/10.1016/s0008-6363(00)00158-9).

- [23] Turner NA, Porter KE. Function and fate of myofibroblasts after myocardial infarction. *Fibrogenesis & Tissue Repair*. 2013 Mar;6(1). Available from: <https://doi.org/10.1186/1755-1536-6-5>.
- [24] Prabhu SD, Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction. *Circulation Research*. 2016 Jun;119(1):91–112. Available from: <https://doi.org/10.1161/circresaha.116.303577>.
- [25] Jugdutt BI. Pleiotropic effects of cardiac drugs on healing post-MI. The good, bad, and ugly. *Heart Failure Reviews*. 2008 Feb;13(4):439–452. Available from: <https://doi.org/10.1007/s10741-008-9090-1>.
- [26] Kim NN, Villarreal FJ, Printz MP, Lee AA, Dillmann WH. Trophic effects of angiotensin II on neonatal rat cardiac myocytes are mediated by cardiac fibroblasts. *American Journal of Physiology-Endocrinology and Metabolism*. 1995 Sep;269(3):E426–E437. Available from: <https://doi.org/10.1152/ajpendo.1995.269.3.e426>.
- [27] Kim S, Ohta K, Hamaguchi A, Yukimura T, Miura K, Iwao H. Angiotensin II Induces Cardiac Phenotypic Modulation and Remodeling In Vivo in Rats. *Hypertension*. 1995 Jun;25(6):1252–1259. Available from: <https://doi.org/10.1161/01.hyp.25.6.1252>.
- [28] Beygui F, Collet JP, Benoliel JJ, Vignolles N, Dumaine R, Barthelemy O, et al. High Plasma Aldosterone Levels on Admission Are Associated With Death in Patients Presenting With Acute ST-Elevation Myocardial Infarction. *Circulation*. 2006 Dec;114(24):2604–2610. Available from: <https://doi.org/10.1161/circulationaha.106.634626>.
- [29] Ishii H, Amano T, Matsubara T, Murohara T. Pharmacological Intervention for Prevention of Left Ventricular Remodeling and Improving Prognosis in Myocardial Infarction. *Circulation*. 2008 Dec;118(25):2710–2718. Available from: <https://doi.org/10.1161/circulationaha.107.748772>.
- [30] Beygui F, Belle EV, Ecollan P, Machecourt J, Hamm CW, Sa ELD, et al. Individual participant data analysis of two trials on aldosterone blockade in myocardial infarction. *Heart*. 2018 Apr;104(22):1843–1849. Available from: <https://doi.org/10.1136/heartjnl-2018-312950>.
- [31] Watson A, Hood S, May C. MECHANISMS OF SYMPATHETIC ACTIVATION IN HEART FAILURE. *Clinical and Experimental Pharmacology and Physiology*. 2006 Dec;33(12):1269–1274. Available from: <https://doi.org/10.1111/j.1440-1681.2006.04523.x>.
- [32] Brodde OE, Michel M. Adrenergic and Muscarinic Receptors in the Human Heart. *Pharmacological Reviews*. 1999;51(4):651–690.
- [33] McDonald TF, Pelzer S, Trautwein W, Pelzer DJ. Regulation and modulation of calcium channels in cardiac, skeletal, and smooth muscle cells. *Physiological Reviews*. 1994 Apr;74(2):365–507. Available from: <https://doi.org/10.1152/physrev.1994.74.2.365>.

- [34] Bünemann M, Gerhardstein BL, Gao T, Hosey MM. Functional Regulation of L-type Calcium Channels via Protein Kinase A-mediated Phosphorylation of the 2Subunit. *Journal of Biological Chemistry*. 1999 Nov;274(48):33851–33854. Available from: <https://doi.org/10.1074/jbc.274.48.33851>.
- [35] Zhang R, Zhao J, Mandveno A, Potter JD. Cardiac Troponin I Phosphorylation Increases the Rate of Cardiac Muscle Relaxation. *Circulation Research*. 1995 Jun;76(6):1028–1035.
- [36] Robertson SP, Johnson JD, Holroyde MJ, Kranias EG, Potter JD, Solaro RJ. The Effect of Troponin I Phosphorylation on the Ca<sup>2+</sup>-binding Properties of the Ca<sup>2+</sup>-regulatory Site of Bovine Cardiac Troponin. *The Journal of Biological Chemistry*. 1982;257(1):260–263.
- [37] Kentish JC, McCloskey DT, Layland J, Palmer S, Leiden JM, Martin AF, et al. Phosphorylation of Troponin I by Protein Kinase A Accelerates Relaxation and Cross-bridge Cycle Kinetics in Mouse Ventricular Muscle. *Circulation Research*. 2001 May;88(10):1059–1065.
- [38] Yamasaki R, Wu Y, McNabb M, Greaser M, Labeit S, Granzier H. Protein Kinase A Phosphorylates Titin's Cardiac-Specific N2B Domain and Reduces Passive Tension in Rat Cardiac Myocytes. *Circulation Research*. 2002 Jun;90(11):1181–1188.
- [39] Colson BA, Bekyarova T, Locher MR, Fitzsimons DP, Irving TC, Moss RL. Protein Kinase A-Mediated Phosphorylation of cMyBP-C Increases Proximity of Myosin Heads to Actin in Resting Myocardium. *Circulation Research*. 2008 Aug;103(3):244–251.
- [40] Lymperopoulos A, Rengo G, Koch WJ. Adrenergic Nervous System in Heart Failure. *Circulation Research*. 2013 Aug;113(6):739–753. Available from: <https://doi.org/10.1161/circresaha.113.300308>.
- [41] de Lucia C, Eguchi A, Koch WJ. New Insights in Cardiac -Adrenergic Signaling During Heart Failure and Aging. *Frontiers in Pharmacology*. 2018 Aug;9. Available from: <https://doi.org/10.3389/fphar.2018.00904>.
- [42] Bürger A, Benicke M, Deten A, Zimmer HG. Catecholamines stimulate interleukin-6 synthesis in rat cardiac fibroblasts. *American Journal of Physiology-Heart and Circulatory Physiology*. 2001 Jul;281(1):H14–H21. Available from: <https://doi.org/10.1152/ajpheart.2001.281.1.h14>.
- [43] Leicht M, Briest W, Zimmer HG. Regulation of norepinephrine-induced proliferation in cardiac fibroblasts by interleukin-6 and p42/p44 mitogen activated protein kinase. *Molecular and Cellular Biochemistry*. 2003;243(1/2):65–72. Available from: <https://doi.org/10.1023/a:1021655023870>.
- [44] Turner N. Chronic 2-adrenergic receptor stimulation increases proliferation of human cardiac fibroblasts via an autocrine mechanism. *Cardiovascular Research*. 2003 Mar;57(3):784–792. Available from: [https://doi.org/10.1016/s0008-6363\(02\)00729-0](https://doi.org/10.1016/s0008-6363(02)00729-0).

- [45] Osadchii OE, Norton GR, McKechnie R, Deftereos D, Woodiwiss AJ. Cardiac dilatation and pump dysfunction without intrinsic myocardial systolic failure following chronic -adrenoreceptor activation. *American Journal of Physiology-Heart and Circulatory Physiology*. 2007 Apr;292(4):H1898–H1905. Available from: <https://doi.org/10.1152/ajpheart.00740.2006>.
- [46] Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, et al. Apoptosis in the Failing Human Heart. *New England Journal of Medicine*. 1997 Apr;336(16):1131–1141. Available from: <https://doi.org/10.1056/nejm199704173361603>.
- [47] Kasama S, Furuya M, Toyama T, Ichikawa S, Kurabayashi M. Effect of atrial natriuretic peptide on left ventricular remodelling in patients with acute myocardial infarction. *European Heart Journal*. 2008 Jan;29(12):1485–1494. Available from: <https://doi.org/10.1093/eurheartj/ehn206>.
- [48] Ulla A, Mohamed MK, Sikder B, Rahman AT, Sumi FA, Hossain M, et al. Coenzyme Q10 prevents oxidative stress and fibrosis in isoprenaline induced cardiac remodeling in aged rats. *BMC Pharmacology and Toxicology*. 2017 Apr;18(1). Available from: <https://doi.org/10.1186/s40360-017-0136-7>.
- [49] Singh RB, Niaz MA, Sharma JP, Kumar R, Bishnoi I, Begom R. Plasma levels of antioxidant vitamins and oxidative stress in patients with acute myocardial infarction. *Acta Cardiol*. 1994;49(5):441–452.
- [50] Grech ED, Jackson MJ, Ramsdale DR. Reperfusion injury after acute myocardial infarction. *BMJ*. 1995 Feb;310(6978):477–478. Available from: <https://doi.org/10.1136/bmj.310.6978.477>.
- [51] Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. *Journal of the American College of Cardiology*. 2000 Mar;35(3):569–582. Available from: [https://doi.org/10.1016/s0735-1097\(99\)00630-0](https://doi.org/10.1016/s0735-1097(99)00630-0).
- [52] Bolognese L, Neskovic AN, Parodi G, Cerisano G, Buonamici P, Santoro GM, et al. Left Ventricular Remodeling After Primary Coronary Angioplasty. *Circulation*. 2002 Oct;106(18):2351–2357. Available from: <https://doi.org/10.1161/01.cir.0000036014.90197.fa>.
- [53] Sutton MSJ, Pfeffer MA, Plappert T, Rouleau JL, Moyé LA, Dagenais GR, et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. *Circulation*. 1994 Jan;89(1):68–75. Available from: <https://doi.org/10.1161/01.cir.89.1.68>.
- [54] Bellenger N, Davies LC, Francis J, Coats A, Pennell D. Reduction in Sample Size for Studies of Remodeling in Heart Failure by the Use of Cardiovascular Magnetic Resonance. *Journal of Cardiovascular Magnetic Resonance*. 2000 Nov;2(4):271–278. Available from: <https://doi.org/10.3109/10976640009148691>.

- [55] Joyce E, Hoogslag GE, Leong DP, Debonnaire P, Katsanos S, Boden H, et al. Association Between Left Ventricular Global Longitudinal Strain and Adverse Left Ventricular Dilatation After ST-Segment–Elevation Myocardial Infarction. *Circulation: Cardiovascular Imaging*. 2014 Jan;7(1):74–81. Available from: <https://doi.org/10.1161/circimaging.113.000982>.
- [56] Bochenek T, Wita K, Tabor Z, Grabka M, Krzych Ł, Wróbel W, et al. Value of Speckle-Tracking Echocardiography for Prediction of Left Ventricular Remodeling in Patients with ST-Elevation Myocardial Infarction Treated by Primary Percutaneous Intervention. *Journal of the American Society of Echocardiography*. 2011 Dec;24(12):1342–1348. Available from: <https://doi.org/10.1016/j.echo.2011.09.003>.
- [57] Abate E, Hoogslag GE, Leong DP, Bertini M, Antoni ML, Nucifora G, et al. Association between Multilayer Left Ventricular Rotational Mechanics and the Development of Left Ventricular Remodeling after Acute Myocardial Infarction. *Journal of the American Society of Echocardiography*. 2014 Mar;27(3):239–248. Available from: <https://doi.org/10.1016/j.echo.2013.12.009>.
- [58] Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuva AN, Treibel TA, et al. Automated Extracellular Volume Fraction Mapping Provides Insights Into the Pathophysiology of Left Ventricular Remodeling Post–Reperfused ST-Elevation Myocardial Infarction. *Journal of the American Heart Association*. 2016 Jul;5(7). Available from: <https://doi.org/10.1161/jaha.116.003555>.
- [59] Carrick D, Haig C, Rauhalammi S, Ahmed N, Mordi I, McEntegart M, et al. Prognostic significance of infarct core pathology revealed by quantitative non-contrast in comparison with contrast cardiac magnetic resonance imaging in reperfused ST-elevation myocardial infarction survivors. *European Heart Journal*. 2015 Aug;37(13):1044–1059. Available from: <https://doi.org/10.1093/eurheartj/ehv372>.
- [60] Masci PG, Ganame J, Francone M, Desmet W, Lorenzoni V, Iacucci I, et al. Relationship between location and size of myocardial infarction and their reciprocal influences on post-infarction left ventricular remodelling. *European Heart Journal*. 2011 Mar;32(13):1640–1648. Available from: <https://doi.org/10.1093/eurheartj/ehr064>.
- [61] Bodi V, Monmeneu JV, Ortiz-Perez JT, Lopez-Lereu MP, Bonanad C, Husser O, et al. Prediction of Reverse Remodeling at Cardiac MR Imaging Soon after First ST-Segment–Elevation Myocardial Infarction: Results of a Large Prospective Registry. *Radiology*. 2016 Jan;278(1):54–63. Available from: <https://doi.org/10.1148/radiol.2015142674>.
- [62] Bulluck H, Rosmini S, Abdel-Gadir A, White SK, Bhuva AN, Treibel TA, et al. Residual Myocardial Iron Following Intramyocardial Hemorrhage During the Convalescent Phase of Reperfused ST-Segment–Elevation Myocardial Infarction and Adverse Left Ventricular Remodeling. *Circulation: Cardiovascular Imaging*. 2016 Oct;9(10). Available from: <https://doi.org/10.1161/circimaging.116.004940>.

- [63] von Lueder TG, Wang BH, Kompa AR, Huang L, Webb R, Jordaan P, et al. Angiotensin Receptor Neprilysin Inhibitor LCZ696 Attenuates Cardiac Remodeling and Dysfunction After Myocardial Infarction by Reducing Cardiac Fibrosis and Hypertrophy. *Circulation: Heart Failure*. 2015 Jan;8(1):71–78. Available from: <https://doi.org/10.1161/circheartfailure.114.001785>.
- [64] Podlesnikar T, Pizarro G, Fernández-Jiménez R, Montero-Cabezas JM, Greif N, Sánchez-González J, et al. Left ventricular functional recovery of infarcted and remote myocardium after ST-segment elevation myocardial infarction (METOCARD-CNIC randomized clinical trial substudy). *J Cardiovasc Magn Reson*. 2020;22(1):44.
- [65] Bethke A, Shanmuganathan L, Andersen GØ, Eritsland J, Swanson D, Kløw NE, et al. Microvascular perfusion in infarcted and remote myocardium after successful primary PCI: angiographic and CMR findings. *European Radiology*. 2018 Jul;29(2):941–950. Available from: <https://doi.org/10.1007/s00330-018-5588-7>.
- [66] Biesbroek PS, Amier RP, Teunissen PFA, Hofman MBM, Robbers LFHJ, van de Ven PM, et al. Changes in remote myocardial tissue after acute myocardial infarction and its relation to cardiac remodeling: A CMR T1 mapping study. *PLOS ONE*. 2017 Jun;12(6):e0180115. Available from: <https://doi.org/10.1371/journal.pone.0180115>.
- [67] Legallois D, Belin A, Nesterov SV, Milliez P, Parienti JJ, Knuuti J, et al. Cardiac rehabilitation improves coronary endothelial function in patients with heart failure due to dilated cardiomyopathy: A positron emission tomography study. *European Journal of Preventive Cardiology*. 2014 Dec;23(2):129–136. Available from: <https://doi.org/10.1177/2047487314565739>.
- [68] Meris A, Amigoni M, Uno H, Thune JJ, Verma A, Kober L, et al. Left atrial remodelling in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo Study. *European Heart Journal*. 2008 Jul;30(1):56–65. Available from: <https://doi.org/10.1093/eurheartj/ehn499>.
- [69] Møller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left Atrial Volume. *Circulation*. 2003 May;107(17):2207–2212. Available from: <https://doi.org/10.1161/01.cir.0000066318.21784.43>.
- [70] Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. *Cardiovascular Ultrasound*. 2009 Feb;7(1). Available from: <https://doi.org/10.1186/1476-7120-7-6>.
- [71] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography*. 2005 Dec;18(12):1440–1463. Available from: <https://doi.org/10.1016/j.echo.2005.10.005>.

- [72] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*. 2016 Apr;29(4):277–314. Available from: <https://doi.org/10.1016/j.echo.2016.01.011>.
- [73] Badano LP, Kolas TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European Heart Journal - Cardiovascular Imaging*. 2018 Mar;19(6):591–600. Available from: <https://doi.org/10.1093/ehjci/jey042>.
- [74] Nucifora G, Marsan NA, Bertini M, Delgado V, Siebelink HMJ, van Werkhoven JM, et al. Reduced Left Ventricular Torsion Early After Myocardial Infarction Is Related to Left Ventricular Remodeling. *Circulation: Cardiovascular Imaging*. 2010 Jul;3(4):433–442. Available from: <https://doi.org/10.1161/circimaging.109.926196>.
- [75] Spinelli L, Morisco C, di Panzillo EA, Izzo R, Trimarco B. Reverse left ventricular remodeling after acute myocardial infarction: the prognostic impact of left ventricular global torsion. *The International Journal of Cardiovascular Imaging*. 2012 Nov;29(4):787–795. Available from: <https://doi.org/10.1007/s10554-012-0159-5>.
- [76] Na HM, Cho GY, Lee JM, Cha MJ, Yoon YE, Lee SP, et al. Echocardiographic Predictors for Left Ventricular Remodeling after Acute ST Elevation Myocardial Infarction with Low Risk Group: Speckle Tracking Analysis. *Journal of Cardiovascular Ultrasound*. 2016;24(2):128. Available from: <https://doi.org/10.4250/jcu.2016.24.2.128>.
- [77] Hsiao JF, Chung CM, Chu CM, Lin YS, Pan KL, Chang ST, et al. Two-Dimensional Speckle Tracking Echocardiography Predict Left Ventricular Remodeling after Acute Myocardial Infarction in Patients with Preserved Ejection Fraction. *PLOS ONE*. 2016 Dec;11(12):e0168109. Available from: <https://doi.org/10.1371/journal.pone.0168109>.
- [78] Prasad SB, Lin A, Kwan C, Sippel J, Younger JF, Hammett C, et al. Determinants of Diastolic Dysfunction Following Myocardial Infarction: Evidence for Causation Beyond Infarct Size. *Heart, Lung and Circulation*. 2020 Jun; Available from: <https://doi.org/10.1016/j.hlc.2020.04.016>.
- [79] Khumri TM, Reid KJ, Kosiborod M, Spertus JA, Main ML. Usefulness of Left Ventricular Diastolic Dysfunction as a Predictor of One-Year Rehospitalization in Survivors of Acute Myocardial Infarction. *The American Journal of Cardiology*. 2009 Jan;103(1):17–21. Available from: <https://doi.org/10.1016/j.amjcard.2008.08.049>.
- [80] Greenberg NL, Vandervoort PM, Firstenberg MS, Garcia MJ, Thomas JD. Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. *American Journal of Physiology-Heart and Circulatory Physiology*. 2001 Jun;280(6):H2507–H2515. Available from: <https://doi.org/10.1152/ajpheart.2001.280.6.h2507>.

- [81] Rademakers FE, Buchalter MB, Rogers WJ, Zerhouni EA, Weisfeldt ML, Weiss JL, et al. Dissociation between left ventricular untwisting and filling. Accentuation by catecholamines. *Circulation*. 1992 Apr;85(4):1572–1581. Available from: <https://doi.org/10.1161/01.cir.85.4.1572>.
- [82] Hodzic A, Bonnefous O, Langet H, Hamiche W, Chaufourier L, Tournoux F, et al. Analysis of inter-system variability of systolic and diastolic intraventricular pressure gradients derived from color Doppler M-mode echocardiography. *Scientific Reports*. 2020 Apr;10(1). Available from: <https://doi.org/10.1038/s41598-020-64059-4>.
- [83] Steine K, Stugaard M, Smiseth OA. Mechanisms of diastolic intraventricular regional pressure differences and flow in the inflow and outflow tracts. *Journal of the American College of Cardiology*. 2002 Sep;40(5):983–990. Available from: [https://doi.org/10.1016/s0735-1097\(02\)02046-6](https://doi.org/10.1016/s0735-1097(02)02046-6).
- [84] Ohara T, Niebel CL, Stewart KC, Charonko JJ, Pu M, Vlachos PP, et al. Loss of Adrenergic Augmentation of Diastolic Intra-LV Pressure Difference in Patients With Diastolic Dysfunction. *JACC: Cardiovascular Imaging*. 2012 Sep;5(9):861–870. Available from: <https://doi.org/10.1016/j.jcmg.2012.05.013>.
- [85] Firstenberg MS, Vandervoort PM, Greenberg NL, Smedira NG, McCarthy PM, Garcia MJ, et al. Noninvasive estimation of transmitral pressure drop across the normal mitral valve in humans: importance of convective and inertial forces during left ventricular filling. *Journal of the American College of Cardiology*. 2000 Nov;36(6):1942–1949. Available from: [https://doi.org/10.1016/s0735-1097\(00\)00963-3](https://doi.org/10.1016/s0735-1097(00)00963-3).
- [86] Hodzic A, Bonnefous O, Langet H, Hamiche W, Chaufourier L, Tournoux F, et al. Analysis of inter-system variability of systolic and diastolic intraventricular pressure gradients derived from color Doppler M-mode echocardiography. *Scientific Reports*. 2020 Apr;10(1). Available from: <https://doi.org/10.1038/s41598-020-64059-4>.
- [87] Courtois M, Kovács SJ, Ludbrook PA. Physiological early diastolic intraventricular pressure gradient is lost during acute myocardial ischemia. *Circulation*. 1990 May;81(5):1688–1696. Available from: <https://doi.org/10.1161/01.cir.81.5.1688>.
- [88] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal – Cardiovascular Imaging*. 2015 Feb;16(3):233–271. Available from: <https://doi.org/10.1093/ehjci/jev014>.
- [89] Savoye C, Equine O, Tricot O, Nogue O, Segrestin B, Sautière K, et al. Left Ventricular Remodeling After Anterior Wall Acute Myocardial Infarction in Modern Clinical Practice (from the REmodelage VEntriculaire [REVE] Study Group). *The American Journal of Cardiology*. 2006 Nov;98(9):1144–1149. Available from: <https://doi.org/10.1016/j.amjcard.2006.06.011>.
- [90] Garcia D. Robust smoothing of gridded data in one and higher dimensions with missing values. *Computational Statistics & Data Analysis*. 2010 Apr;54(4):1167–1178. Available from: <https://doi.org/10.1016/j.csda.2009.09.020>.

- [91] Muth S, Dort S, Sebag IA, Blais MJ, Garcia D. Unsupervised dealiasing and denoising of color-Doppler data. *Medical Image Analysis*. 2011 Aug;15(4):577–588. Available from: <https://doi.org/10.1016/j.media.2011.03.003>.
- [92] Firstenberg MS, Greenberg NL, Garcia MJ, Thomas JD. Relationship Between Ventricular Contractility and Early Diastolic Intraventricular Pressure Gradients: A Diastolic Link to Systolic Function. *Journal of the American Society of Echocardiography*. 2008 May;21(5):501–506. Available from: <https://doi.org/10.1016/j.echo.2007.08.023>.
- [93] Stugaard M, Smiseth OA, Risøe C, Ihlen H. Intraventricular early diastolic filling during acute myocardial ischemia, assessment by multigated color m-mode Doppler echocardiography. *Circulation*. 1993 Dec;88(6):2705–2713. Available from: <https://doi.org/10.1161/01.cir.88.6.2705>.
- [94] Villemain O, Correia M, Mousseaux E, Baranger J, Zarka S, Podetti I, et al. Myocardial Stiffness Evaluation Using Noninvasive Shear Wave Imaging in Healthy and Hypertrophic Cardiomyopathic Adults. *JACC: Cardiovascular Imaging*. 2019 Jul;12(7):1135–1145. Available from: <https://doi.org/10.1016/j.jcmg.2018.02.002>.
- [95] Beyar R, Sideman S. Left ventricular mechanics related to the local distribution of oxygen demand throughout the wall. *Circulation Research*. 1986 May;58(5):664–677. Available from: <https://doi.org/10.1161/01.res.58.5.664>.
- [96] Tibayan FA. Alterations in Left Ventricular Torsion and Diastolic Recoil After Myocardial Infarction With and Without Chronic Ischemic Mitral Regurgitation. *Circulation*. 2004 Sep;110(11\_suppl\_1):II–109–II–114. Available from: <https://doi.org/10.1161/01.cir.0000138385.05471.41>.
- [97] Bonios MJ, Kaladaridou A, Tasoulis A, Papadopoulou E, Pamboukas C, Ntalianis A, et al. Value of apical circumferential strain in the early post-myocardial infarction period for prediction of left ventricular remodeling. *Hellenic J Cardiol*. 2014;55(4):305–3012.
- [98] Buono F, Spinelli L, Giallauria F, di Panzillo EA, Marino SD, Ferrara F, et al. Usefulness of Satisfactory Control of Low-Density Lipoprotein Cholesterol to Predict Left Ventricular Remodeling After a First ST-Elevation Myocardial Infarction Successfully Reperfused†. *The American Journal of Cardiology*. 2011 Jun;107(12):1772–1778. Available from: <https://doi.org/10.1016/j.amjcard.2011.01.066>.
- [99] Carrabba N, Parodi G, Valenti R, Migliorini A, Bellandi B, Antoniucci D. Prognostic value of reverse left ventricular remodeling after primary angioplasty for STEMI. *Atherosclerosis*. 2012 May;222(1):123–128. Available from: <https://doi.org/10.1016/j.atherosclerosis.2012.02.028>.
- [100] Cerisano G, Buonamici P, Parodi G, Santini A, Moschi G, Valenti R, et al. Early changes of left ventricular filling pattern after reperfused ST-elevation myocardial infarction and doxycycline therapy: Insights from the TIPTOP trial. *International Journal of Cardiology*. 2017 Aug;240:43–48. Available from: <https://doi.org/10.1016/j.ijcard.2017.03.125>.

- [101] Joyce E, Hoogslag GE, Leong DP, Fox K, Schali J MJ, Marsan NA, et al. Association between discharge heart rate and left ventricular adverse remodelling in ST segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *Heart*. 2013 Mar;99(8):556–561. Available from: <https://doi.org/10.1136/heartjnl-2012-303406>.
- [102] Haldón JL, Quero MF, Mancha F, Urbano JA, Guisado A, Villa M, et al. Value of NT-ProBNP Level and Echocardiographic Parameters in ST-Segment Elevation Myocardial Infarction Treated by Primary Angioplasty: Relationships Between These Variables and Their Usefulness as Predictors of Ventricular Remodeling. *Revista Española de Cardiología (English Edition)*. 2010 Jan;63(9):1019–1027. Available from: [https://doi.org/10.1016/s1885-5857\(10\)70205-x](https://doi.org/10.1016/s1885-5857(10)70205-x).
- [103] Lacalzada J, de la Rosa A, Izquierdo MM, Jiménez JJ, Iribarren JL, García-González MJ, et al. Left ventricular global longitudinal systolic strain predicts adverse remodeling and subsequent cardiac events in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. *The International Journal of Cardiovascular Imaging*. 2015 Jan;31(3):575–584. Available from: <https://doi.org/10.1007/s10554-015-0593-2>.
- [104] Fertin M, Dubois E, Belliard A, Amouyel P, Pinet F, Bauters C. Usefulness of Circulating Biomarkers for the Prediction of Left Ventricular Remodeling After Myocardial Infarction. *The American Journal of Cardiology*. 2012 Jul;110(2):277–283. Available from: <https://doi.org/10.1016/j.amjcard.2012.02.069>.
- [105] Cruden NLM, Fox KAA, Ludlam CA, Johnston NR, Newby DE. Neutral Endopeptidase Inhibition Augments Vascular Actions of Bradykinin in Patients Treated With Angiotensin-Converting Enzyme Inhibition. *Hypertension*. 2004 Dec;44(6):913–918. Available from: <https://doi.org/10.1161/01.hyp.0000146483.78994.56>.
- [106] Wilkinson IB, McEniery CM, Bongaerts KH, MacCallum H, Webb DJ, Cockcroft JR. Adrenomedullin (ADM) in the human forearm vascular bed: effect of neutral endopeptidase inhibition and comparison with proadrenomedullin NH2-terminal 20 peptide (PAMP). *British Journal of Clinical Pharmacology*. 2001 Dec;52(2):159–164. Available from: <https://doi.org/10.1046/j.0306-5251.2001.1420.x>.
- [107] McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *New England Journal of Medicine*. 2014 Sep;371(11):993–1004. Available from: <https://doi.org/10.1056/nejmoa1409077>.
- [108] Solomon SD, Skali H, Anavekar NS, Bourgon M, Barvik S, Ghali JK, et al. Changes in Ventricular Size and Function in Patients Treated With Valsartan, Captopril, or Both After Myocardial Infarction. *Circulation*. 2005 Jun;111(25):3411–3419. Available from: <https://doi.org/10.1161/circulationaha.104.508093>.
- [109] Indications for ACE Inhibitors in the Early Treatment of Acute Myocardial Infarction. *Circulation*. 1998 Jun;97(22):2202–2212. Available from: <https://doi.org/10.1161/01.cir.97.22.2202>.

- [110] Yellon DM, Hausenloy DJ. Myocardial Reperfusion Injury. *New England Journal of Medicine*. 2007 Sep;357(11):1121–1135. Available from: <https://doi.org/10.1056/nejmra071667>.
- [111] Ibáñez B, Heusch G, Ovize M, de Werf FV. Evolving Therapies for Myocardial Ischemia/Reperfusion Injury. *Journal of the American College of Cardiology*. 2015 Apr;65(14):1454–1471. Available from: <https://doi.org/10.1016/j.jacc.2015.02.032>.
- [112] Khan AR, Binabdulhak AA, Alastal Y, Khan S, Faricy-Beredo BM, Luni FK, et al. Cardioprotective role of ischemic postconditioning in acute myocardial infarction: A systematic review and meta-analysis. *American Heart Journal*. 2014 Oct;168(4):512–521.e4. Available from: <https://doi.org/10.1016/j.ahj.2014.06.021>.
- [113] Rababa'h AM, Guillory AN, Mustafa R, Hijjawi T. Oxidative Stress and Cardiac Remodeling: An Updated Edge. *Current Cardiology Reviews*. 2018 Mar;14(1):53–59. Available from: <https://doi.org/10.2174/1573403x14666180111145207>.
- [114] Kaurola P, Sharma V, Vonk A, Vattulainen I, Róg T. Distribution and dynamics of quinones in the lipid bilayer mimicking the inner membrane of mitochondria. *Biochimica et Biophysica Acta (BBA) - Biomembranes*. 2016 Sep;1858(9):2116–2122. Available from: <https://doi.org/10.1016/j.bbamem.2016.06.016>.
- [115] Lenaz G, Fato R, Formiggini G, Genova ML. The role of Coenzyme Q in mitochondrial electron transport. *Mitochondrion*. 2007 Jun;7:S8–S33. Available from: <https://doi.org/10.1016/j.mito.2007.03.009>.
- [116] Bentinger M, Brismar K, Dallner G. The antioxidant role of coenzyme Q. *Mitochondrion*. 2007 Jun;7:S41–S50. Available from: <https://doi.org/10.1016/j.mito.2007.02.006>.
- [117] Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. *Biochimica et Biophysica Acta (BBA) - Biomembranes*. 2004 Jan;1660(1-2):171–199. Available from: <https://doi.org/10.1016/j.bbamem.2003.11.012>.
- [118] Legallois D, Hodzic A, Alexandre J, Dolladille C, Saloux E, Manrique A, et al. Definition of left ventricular remodelling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade. *Heart Failure Reviews*. 2020 May; Available from: <https://doi.org/10.1007/s10741-020-09975-3>.
- [119] Bulluck H, Dharmakumar R, Arai AE, Berry C, Hausenloy DJ. Cardiovascular Magnetic Resonance in Acute ST-Segment-Elevation Myocardial Infarction. *Circulation*. 2018 May;137(18):1949–1964. Available from: <https://doi.org/10.1161/circulationaha.117.030693>.
- [120] Klem I, Heiberg E, Assche LV, Parker MA, Kim HW, Grizzard JD, et al. Sources of variability in quantification of cardiovascular magnetic resonance infarct size - reproducibility among three core laboratories. *Journal of Cardiovascular Magnetic Resonance*. 2017 Aug;19(1). Available from: <https://doi.org/10.1186/s12968-017-0378-y>.

- [121] Belle L, Cayla G, Cottin Y, Coste P, Khalife K, Labèque JN, et al. French Registry on Acute ST-elevation and non-ST-elevation Myocardial Infarction 2015 (FAST-MI 2015). Design and baseline data. *Archives of Cardiovascular Diseases*. 2017 Jun;110(6-7):366–378. Available from: <https://doi.org/10.1016/j.acvd.2017.05.001>.
- [122] Meng L, Wang J, hui Ding W, Han P, Yang Y, tong Qi L, et al. Plasma catestatin level in patients with acute myocardial infarction and its correlation with ventricular remodelling. *Postgraduate Medical Journal*. 2012 Dec;89(1050):193–196. Available from: <https://doi.org/10.1136/postgradmedj-2012-131060>.
- [123] Choi H, Yoo BS, Doh JH, Yoon HJ, Ahn MS, Kim JY, et al. The optimal time of B-type natriuretic peptide sampling associated with post-myocardial infarction remodelling after primary percutaneous coronary intervention : cardiovascular topics. *Cardiovascular Journal Of Africa*. 2013 Aug;24(5):165–170. Available from: <https://doi.org/10.5830/cvja-2013-024>.
- [124] Swiatkiewicz I, Kozinski M, Magielski P, Fabiszak T, Sukiennik A, Navarese EP, et al. Value of C-Reactive Protein in Predicting Left Ventricular Remodelling in Patients with a First ST-Segment Elevation Myocardial Infarction. *Mediators of Inflammation*. 2012;2012:1–11. Available from: <https://doi.org/10.1155/2012/250867>.
- [125] Urbano-Moral JA, Lopez-Haldon JE, Fernandez M, Mancha F, Sanchez A, Rodriguez-Puras MJ, et al. Prognostic value of different serum biomarkers for left ventricular remodelling after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. 2012 May;98(15):1153–1159. Available from: <https://doi.org/10.1136/heartjnl-2012-301636>.
- [126] Sutton MSJ, Pfeffer MA, Moye L, Plappert T, Rouleau JL, Lamas G, et al. Cardiovascular Death and Left Ventricular Remodeling Two Years After Myocardial Infarction. *Circulation*. 1997 Nov;96(10):3294–3299. Available from: <https://doi.org/10.1161/01.cir.96.10.3294>.
- [127] Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet*. 2003 Jan;361(9351):13–20. Available from: [https://doi.org/10.1016/s0140-6736\(03\)12113-7](https://doi.org/10.1016/s0140-6736(03)12113-7).
- [128] Reindl M, Reinstadler SJ, Tiller C, Feistritzer HJ, Kofler M, Brix A, et al. Prognosis-based definition of left ventricular remodeling after ST-elevation myocardial infarction. *European Radiology*. 2018 Dec;29(5):2330–2339. Available from: <https://doi.org/10.1007/s00330-018-5875-3>.
- [129] Rodriguez-Palomares JF, Gavara J, Ferreira-González I, Valente F, Rios C, Rodríguez-García J, et al. Prognostic Value of Initial Left Ventricular Remodeling in Patients With Reperfused STEMI. *JACC: Cardiovascular Imaging*. 2019 Dec;12(12):2445–2456. Available from: <https://doi.org/10.1016/j.jcmg.2019.02.025>.
- [130] Masci PG, Pavon AG, Pontone G, Symons R, Lorenzoni V, Francone M, et al. Early or deferred cardiovascular magnetic resonance after ST-segment-elevation myocardial infarction for effective risk stratification. *European Heart Journal - Cardiovascular Imaging*. 2019 Jul;21(6):632–639. Available from: <https://doi.org/10.1093/ehjci/jez179>.

- [131] Grothues F, Smith GC, Moon JCC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *The American Journal of Cardiology*. 2002 Jul;90(1):29–34. Available from: [https://doi.org/10.1016/s0002-9149\(02\)02381-0](https://doi.org/10.1016/s0002-9149(02)02381-0).
- [132] van der Bijl P, Abou R, Goedemans L, Gersh BJ, Holmes DR, Marsan NA, et al. Left Ventricular Post-Infarct Remodeling. *JACC: Heart Failure*. 2020 Feb;8(2):131–140. Available from: <https://doi.org/10.1016/j.jchf.2019.08.014>.
- [133] Bulluck H, Go YY, Crimi G, Ludman AJ, Rosmini S, Abdel-Gadir A, et al. Defining left ventricular remodeling following acute ST-segment elevation myocardial infarction using cardiovascular magnetic resonance. *Journal of Cardiovascular Magnetic Resonance*. 2017 Mar;19(1). Available from: <https://doi.org/10.1186/s12968-017-0343-9>.
- [134] Mather AN, Fairbairn TA, Artis NJ, Greenwood JP, Plein S. Timing of Cardiovascular MR Imaging after Acute Myocardial Infarction: Effect on Estimates of Infarct Characteristics and Prediction of Late Ventricular Remodeling. *Radiology*. 2011 Oct;261(1):116–126. Available from: <https://doi.org/10.1148/radiol.11110228>.
- [135] Garcia G, de la Barca JC, Mirebeau-Prunier D, Reynier P, Furber A, Prunier F, et al. Metabolomic Approach in STEMI-Patients Undergoing Left Ventricular Remodeling. *International Journal of Molecular Sciences*. 2019 Jan;20(2):289. Available from: <https://doi.org/10.3390/ijms20020289>.
- [136] Torrado J, Cain C, Mauro AG, Romeo F, Ockaili R, Chau VQ, et al. Sacubitril/Valsartan Averts Adverse Post-Infarction Ventricular Remodeling and Preserves Systolic Function in Rabbits. *Journal of the American College of Cardiology*. 2018 Nov;72(19):2342–2356. Available from: <https://doi.org/10.1016/j.jacc.2018.07.102>.
- [137] Dogan C, Ozdemir N, Hatipoglu S, Bakal RB, Omaygenc MO, Dindar B, et al. Relation of left atrial peak systolic strain with left ventricular diastolic dysfunction and brain natriuretic peptide level in patients presenting with ST-elevation myocardial infarction. *Cardiovascular Ultrasound*. 2013 Jul;11(1). Available from: <https://doi.org/10.1186/1476-7120-11-24>.
- [138] Barbier P, Solomon SB, Schiller NB, Glantz SA. Left Atrial Relaxation and Left Ventricular Systolic Function Determine Left Atrial Reservoir Function. *Circulation*. 1999 Jul;100(4):427–436. Available from: <https://doi.org/10.1161/01.cir.100.4.427>.
- [139] Toma Y, Matsuda Y, Moritani K, Ogawa H, Matsuzaki M, Kusakawa R. Left atrial filling in normal human subjects: relation between left atrial contraction and left atrial early filling. *Cardiovascular Research*. 1987 Apr;21(4):255–259. Available from: <https://doi.org/10.1093/cvr/21.4.255>.
- [140] Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction. *Journal of the American College of Cardiology*. 2019 Apr;73(15):1961–1977. Available from: <https://doi.org/10.1016/j.jacc.2019.01.059>.

- [141] Antoni ML, ten Brinke EA, Marsan NA, Atary JZ, Holman ER, van der Wall EE, et al. Comprehensive Assessment of Changes in Left Atrial Volumes and Function after ST-Segment Elevation Acute Myocardial Infarction: Role of Two-Dimensional Speckle-Tracking Strain Imaging. *Journal of the American Society of Echocardiography*. 2011 Oct;24(10):1126–1133. Available from: <https://doi.org/10.1016/j.echo.2011.06.017>.
- [142] Kühl JT, Kofoed KF, Møller JE, Hammer-Hansen S, Kristensen T, Køber L, et al. Assessment of left atrial volume and mechanical function in ischemic heart disease. *International Journal of Cardiology*. 2010 Nov;145(2):197–202. Available from: <https://doi.org/10.1016/j.ijcard.2009.05.029>.
- [143] DIAMOND G, FORRESTER JS. Effect of Coronary Artery Disease and Acute Myocardial Infarction on Left Ventricular Compliance in Man. *Circulation*. 1972 Jan;45(1):11–19. Available from: <https://doi.org/10.1161/01.cir.45.1.11>.
- [144] Palardy M, Ducharme A, O'Meara E. Inhibiting the renin-angiotensin system with ACE inhibitors or ARBs after MI. *Current Heart Failure Reports*. 2007 Dec;4(4):190–197. Available from: <https://doi.org/10.1007/s11897-007-0012-7>.
- [145] Antoni ML, ten Brinke EA, Atary JZ, Marsan NA, Holman ER, Schaliij MJ, et al. Left atrial strain is related to adverse events in patients after acute myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. 2011 May;97(16):1332–1337. Available from: <https://doi.org/10.1136/hrt.2011.227678>.
- [146] Courtois M, Kovács SJ, Ludbrook PA. Transmitral pressure-flow velocity relation. Importance of regional pressure gradients in the left ventricle during diastole. *Circulation*. 1988 Sep;78(3):661–671. Available from: <https://doi.org/10.1161/01.cir.78.3.661>.
- [147] Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovascular Therapeutics*. 2018 Jun;36(4):e12435. Available from: <https://doi.org/10.1111/1755-5922.12435>.
- [148] Legallois D, Macquaire C, Hodzic A, Allouche S, Khouakhi IE, Manrique A, et al. Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction. *BMC Cardiovascular Disorders*. 2020 Jul;20(1). Available from: <https://doi.org/10.1186/s12872-020-01578-y>.
- [149] Reddy YNV, Iyer SR, Scott CG, Rodeheffer RJ, Bailey K, Jenkins G, et al. Soluble Neprilysin in the General Population: Clinical Determinants and Its Relationship to Cardiovascular Disease. *Journal of the American Heart Association*. 2019 Aug;8(15). Available from: <https://doi.org/10.1161/jaha.119.012943>.
- [150] Bernelin H, Mewton N, Si-Mohamed S, Croisille P, Rioufol G, Bonnefoy-Cudraz E, et al. Neprilysin levels at the acute phase of ST-elevation myocardial infarction. *Clinical Cardiology*. 2018 Dec;42(1):32–38. Available from: <https://doi.org/10.1002/clc.23090>.
- [151] Liang S, Ping Z, Ge J. Coenzyme Q10 Regulates Antioxidative Stress and Autophagy in Acute Myocardial Ischemia-Reperfusion Injury. *Oxidative Medicine and Cellular Longevity*. 2017;2017:1–12. Available from: <https://doi.org/10.1155/2017/9863181>.

- [152] Singh R, Fedacko J, Mojto V, Pella D. Coenzyme Q10 Modulates Remodeling Possibly by Decreasing Angiotensin-Converting Enzyme in Patients with Acute Coronary Syndrome. *Antioxidants*. 2018 Jul;7(8):99. Available from: <https://doi.org/10.3390/antiox7080099>.
- [153] Huang CH, Kuo CL, Huang CS, Tseng WM, Lian IB, Chang CC, et al. High plasma coenzyme Q10 concentration is correlated with good left ventricular performance after primary angioplasty in patients with acute myocardial infarction. *Medicine*. 2016 Aug;95(31):e4501. Available from: <https://doi.org/10.1097/md.0000000000004501>.
- [154] Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL. Coenzyme Q10 in cardiovascular disease. *Mitochondrion*. 2007 Jun;7:S154–S167. Available from: <https://doi.org/10.1016/j.mito.2007.02.005>.
- [155] Sharma A, Fonarow GC, Butler J, Ezekowitz JA, Felker GM. Coenzyme Q10 and Heart Failure. *Circulation: Heart Failure*. 2016 Mar;9(4):e002639. Available from: <https://doi.org/10.1161/circheartfailure.115.002639>.
- [156] Barshop BA, Gangoiti JA. Analysis of coenzyme Q in human blood and tissues. *Mitochondrion*. 2007 Jun;7:S89–S93. Available from: <https://doi.org/10.1016/j.mito.2007.04.002>.
- [157] Niklowitz P, Onur S, Fischer A, Laudes M, Palussen M, Menke T, et al. Coenzyme Q10 serum concentration and redox status in European adults: influence of age, sex, and lipoprotein concentration. *Journal of Clinical Biochemistry and Nutrition*. 2016;58(3):240–245. Available from: <https://doi.org/10.3164/jcbn.15-73>.
- [158] Tomasetti M, Alleva R, Solenghi MD, Littarru GP. Distribution of antioxidants among blood components and lipoproteins: Significance of lipids/CoQ10ratio as a possible marker of increased risk for atherosclerosis. *BioFactors*. 1999;9(2-4):231–240. Available from: <https://doi.org/10.1002/biof.5520090218>.
- [159] Barth E. Ultrastructural quantitation of mitochondria and myofilaments in cardiac muscle from 10 different animal species including man. *Journal of Molecular and Cellular Cardiology*. 1992 Jul;24(7):669–681. Available from: [https://doi.org/10.1016/0022-2828\(92\)93381-s](https://doi.org/10.1016/0022-2828(92)93381-s).
- [160] Alleva R, Tomasetti M, Battino M, Curatola G, Littarru GP, Folkers K. The roles of coenzyme Q10 and vitamin E on the peroxidation of human low density lipoprotein subfractions. *Proceedings of the National Academy of Sciences*. 1995 Sep;92(20):9388–9391. Available from: <https://doi.org/10.1073/pnas.92.20.9388>.
- [161] Bentinger M, Dallner G, Chojnacki T, Swiezewska E. Distribution and breakdown of labeled coenzyme Q10 in rat. *Free Radical Biology and Medicine*. 2003 Mar;34(5):563–575. Available from: [https://doi.org/10.1016/s0891-5849\(02\)01357-6](https://doi.org/10.1016/s0891-5849(02)01357-6).

## **Paramètres biologiques et échocardiographiques et remodelage ventriculaire gauche après syndrome coronarien aigu avec sus-décalage du segment ST**

Biological and echocardiographic parameters and left ventricular remodeling after ST-elevation myocardial infarction

Damien LEGALLOIS

**Résumé** Le remodelage ventriculaire gauche est une complication fréquente des patients ayant présenté un syndrome coronarien aigu, pouvant conduire à terme à une situation d'insuffisance cardiaque. Il est donc important de connaître les facteurs associés à la survenue d'un remodelage ventriculaire afin de dépister plus précocement les patients à plus haut risque d'insuffisance cardiaque et ainsi optimiser leur prise en charge. Ce travail comprend deux axes. Le premier porte sur la recherche de nouveaux paramètres d'imagerie associés à la survenue du remodelage. Nous avons dans un premier temps réalisé une revue de la littérature concernant la définition du remodelage ventriculaire gauche en imagerie par résonance magnétique. Puis, nous avons conduit deux études ayant pour but de rechercher une association entre (i) le strain atrial gauche et, (ii) le gradient de pression intraventriculaire gauche diastolique, évalués en échocardiographie 24-48 heures après le syndrome coronarien aigu et le remodelage ventriculaire gauche au cours du suivi. Le second axe porte sur les biomarqueurs associés au remodelage ventriculaire post-infarctus. Nous avons réalisé une revue de la littérature au sujet des biomarqueurs qui, dosés lors de l'hospitalisation initiale, sont associés à l'existence d'un remodelage lors du suivi. Nous avons ensuite étudié la valeur prédictive de deux biomarqueurs (la néprilysine et le coenzyme Q10) pour la survenue d'un remodelage ventriculaire gauche.

**Abstract** Left ventricular remodeling is a common complication in patients following acute myocardial infarction and may lead to heart failure. Some baseline parameters are associated with remodeling at follow-up, allowing to better discriminate patients with an increased risk of heart failure to optimize therapeutics. This work has two axes, focused on imaging and biological parameters associated with left ventricular remodeling, respectively. First, we reviewed past studies that defined remodeling using cardiac magnetic resonance imaging. Then, we studied the association between some echocardiographic parameters (left atrial strain and diastolic intraventricular pressure gradient) and left ventricular remodeling after ST-elevation myocardial infarction. In the other axis, we reviewed biomarkers that have been associated with left ventricular remodeling in prior studies. Then, we investigated the association between neprilysin and coenzyme Q10 levels and left ventricular remodeling in STEMI patients.

**Mots-clés** remodelage ventriculaire gauche ; syndrome coronarien aigu avec sus-décalage du segment ST ; imagerie par résonance magnétique ; échocardiographie ; strain atrial ; fonction diastolique ; biomarqueurs ; néprilysine ; coenzyme Q10.

**Key-words** left ventricular remodeling ; ST-elevation myocardial infarction ; cardiac magnetic resonance imaging ; echocardiography ; atrial strain ; diastolic function ; biomarkers ; neprilysin ; coenzyme Q10.