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Nouvelles approches épidémiologiques des infarctus du myocarde de type 2 : vers une prise en charge personnalisée

Coffy-Akpolet Yao

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PREPAREE A

EA 7460 : Physiopathologie et Epidémiologie Cérébro-Cardiovasculaires (PEC2)

Ecole doctorale n° ES 554

Ecole Doctorale : Environnements Santé

Doctorat de Médecine, pathologie cardiorespiratoire et vasculaire

Par

M. Hermann YAO

**NOUVELLES APPROCHES EPIDEMIOLOGIQUES DES INFARCTUS DU MYOCARDE DE TYPE 2 :
VERS UNE PRISE EN CHARGE PERSONNALISEE**

Thèse présentée et soutenue à Dijon, le 12 décembre 2023

Composition du Jury :

Monsieur BOCCARA, Franck	Professeur des Universités, Hôpital Saint-Antoine	Rapporteur, Président
Monsieur PUYMIRAT, Etienne	Professeur des Universités, Hôpital Européen Georges Pompidou	Rapporteur
Monsieur COTTIN, Yves	Professeur des Universités, CHU de Dijon	Examineur
Monsieur MONSUEZ, Jean-Jacques	Praticien Hospitalier, Hôpital René Muret	Examineur
Madame ZELLER, Marianne	Professeure des Universités, Université de Bourgogne	Directeur de thèse
Monsieur PUTOT, Alain	Praticien Hospitalier, Hôpitaux du Mont Blanc	Codirecteur de thèse
Monsieur N'GUETTA, Roland	Professeur des Universités, Institut de cardiologie d'Abidjan	Invité

Titre : NOUVELLES APPROCHES EPIDEMIOLOGIQUES DES INFARCTUS DU MYOCARDE DE TYPE 2 : VERS UNE PRISE EN CHARGE PERSONNALISEE.

Mots clés : Maladie coronaire. Athérosclérose. Infarctus du myocarde. Infarctus du myocarde de type 2. Epidémiologie. Pronostic.

Introduction : l'infarctus du myocarde (IDM) de type 2, qui résulte d'un déséquilibre entre les apports et les besoins en oxygène du myocarde en l'absence d'événement athéro-thrombotique, est une entité mal connue. L'objectif de ce travail était de préciser certains aspects épidémiologiques et diagnostiques de l'IDM de type 2, notamment la place de la maladie coronaire, et d'évaluer la pertinence clinique et pronostique d'une nouvelle classification des IDM.

Méthodes : A partir de la base de données de l'Observatoire des Infarctus de la Côte d'Or (RICO), nous avons analysé les données des patients hospitalisés pour un IDM entre 2012 et 2017, après adjudication des IDM de type 1, de type 2 et des sous types identifiés selon la nouvelle classification distinguant les IDM de type 2 avec (IDM de type 2A) et sans maladie coronaire sous-jacente (IDM de type 2B). Nous avons également réalisé une revue systématique de la littérature sur la maladie coronaire obstructive (MCO) dans l'IDM de type 2 à partir de la base de données PubMed®. Enfin, nous avons travaillé sur le REGistre des InfArctus de Côte d'Ivoire (REACTIV) hospitalisés pour un IDM entre 2018 et 2022 à l'Institut de cardiologie d'Abidjan, afin d'identifier les spécificités des IDM de type 2 dans cette population sub-saharienne.

Résultats : Parmi les 4573 patients inclus dans l'observatoire RICO sur une période de 5 ans, 3806 (81,1%) patients et 767 (18,9%) présentaient respectivement un IDM de type 1 et un IDM de type 2 après reclassification. Une coronaropathie obstructive était retrouvée chez 68,6 % des patients atteints d'IDM de type 2.

L'IDM de type 2A concernait des patients plus âgés (âge médian 78 ans), avec davantage de comorbidités, et il était associée à un plus mauvais pronostic à 1 an, comparativement aux IDM de type 2B et aux IDM de type 1 de nature athéro-thrombotique (type 1A). Nos données retrouvent un surrisque, d'environ 40%, pour la mortalité toutes causes (HR 1,362; IC95% 1,029-1,802) de l'IDM de type 2A par rapport à l'IDM de type 1A. La revue systématique nous a permis de monter une prévalence particulièrement variable de la MCO dans l'IDM de type 2 (entre 30 et 92%), dépendante des définitions, du mode diagnostique de la coronaropathie et de l'origine des populations étudiées. Chez des patients admis aux urgences, un antécédent de MCO était un facteur prédictif indépendant de présenter un IDM de type 2 par rapport à un IDM de type 1, avec une augmentation de cette probabilité de près de 40%. Enfin, parmi les patients inclus dans le programme REACTIV, 441(14,1 %) ont présenté un IDM de type 2. Comparativement aux IDM de type 1, les IDM de type 2 avaient une tendance à être plus jeunes (54 vs 58 ans, $p = 0,09$), avec une plus faible fréquence de facteurs de risque cardiovasculaires. Les IDM de type 2 présentaient une MCO moins sévère, avec une atteinte tritonculaire moins fréquente ($p < 0,001$). Dans cette population sub-saharienne, l'embolie coronaire (24,2 %), l'hypertension sévère ± hypertrophie ventriculaire gauche (22,6 %) et la tachyarythmie (16,1 %) constituaient les principaux facteurs déclenchants.

Conclusion : Nos travaux soutiennent l'hypothèse que l'IDM de type 2, souvent considérée comme une pathologie gériatrique, semble en réalité présenter une grande hétérogénéité épidémiologique et physiopathologique. De plus, nous suggérons que l'identification de la maladie coronaire, dont la prévalence est élevée, pourrait permettre d'améliorer la caractérisation et la stratification du risque des IDM de type 2 et ainsi guider le développement d'études interventionnelles pour améliorer leur prise en charge.

Title : NEW EPIDEMIOLOGICAL APPROACHES OF TYPE 2 MYOCARDIAL INFARCTION : TOWARDS PERSONALIZED CARE.

Keywords : Coronary artery disease. Atherosclerosis. Myocardial infarction. Type 2 myocardial infarction. Epidemiology. Prognostic.

Introduction : Type 2 myocardial infarction (MI) resulting from an imbalance between oxygen supply and demand, in the absence of atherothrombotic phenomenon, remains an enigmatic clinical entity. This work aimed to precise type 2 MI epidemiological and prognostic features, especially the key role of coronary artery disease (CAD), and to appraise the clinical and prognostic relevance of a new classification of MI proposed by de Lemos.

Method : Using the Observatoire des Infarctus de la Côte d'Or (RICO), we collected data from MI hospitalizations, after adjudication of type 1 MI and type 2 MI, and sub-groups according to the new classification, with categorization of T2MI into those with (T2AMI) or without (T2BMI) obstructive coronary artery disease (CAD). We also conducted a systematic review of the literature on the role of obstructive CAD in T2MI using the PubMed® database. Finally, we analyzed data from the REgistre des InfArctus de Côte d'Ivoire (REACTIV) at the Abidjan Heart Institute, in order to identify the specific features of type 2 MI in this Sub-Saharan Africa population.

Results : Among the 4573 patients included in RICO over a 5-year period, 3806 (81.1%) and 767 (18.9%) had T1MI and T2MI after reclassification, respectively. Obstructive CAD was identified in 68.6% of patients with T2MI. T2AMI affected older patients (median age 78 yo), with more comorbidities, and is associated with poorer outcomes after 1-year follow-up, compared with T2BMI and even T1MI due to atherothrombosis (T1AMI).

Our data show a 40% excess all-cause mortality at 1-year (HR 1.362; IC95% 1.029-1.802) in T2AMI versus T1AMI. Based on the systematic review of the literature, we found a wide range of CAD prevalence in type 2 MI (between 30% and 92%), depending on definition criteria, diagnostic tools and populations studied. In patients admitted to the emergency department, history of obstructive CAD was an independent predictor of T2MI versus T1MI, increasing this probability by 40% (OR 1.38; 95%CI 1.08-1.77). Finally, of the MI patients included in REACTIV registry over 4 years, 62 (14.1%) met the definition of T2MI. Patients with T2MI were slightly younger (54 vs. 58 years, $p = 0.09$) with fewer conventional CV risk factors. Patients with T2MI had less severe CAD, with less 3-vessel CAD ($p < 0.001$). The main triggering factors for T2MI in this Sub-Saharan population were coronary embolism (24.2%), severe hypertension \pm left ventricular hypertrophy (22.6%) and tachyarrhythmia (16.1%).

Conclusion : Our work supports the hypothesis of epidemiological and pathophysiological heterogeneity of T2MI, despite it is increasingly considered as a geriatric condition. Furthermore, we suggest that the identification of CAD, which is highly prevalent, could improve the characterization and risk stratification of type 2 MI, and help target interventional studies to improve its management and outcomes.

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A tous mes amis.

LISTE DES ABREVIATIONS

ACC : American College of Cardiology

ACT-2 : Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction

AHA : American Heart Association

ATL : angioplastie coronaire transluminale

AUC : aire sous la courbe

CASABLANCA : Catheter Sampled Blood Archive in Cardiovascular Diseases

CHR : centre hospitalier régional

CHU : centre hospitalier universitaire

CI : cardiopathies ischémiques

CK-MB : creatine kinase myocardial band

CV : cardiovasculaire

DAMIN : Dijon-Abidjan Myocardial Infarction

DEFINE TYPE 2 MI : DEFINing the PrEvalence and Characteristics of Coronary Artery Disease Among Patients With TYPE 2 Myocardial Infarction Using CT-FFR

ECG : électrocardiogramme

ESC : European Society of Cardiology

FAST-MI : french registry on acute ST-elevation and non ST-elevation myocardial infarction

FFR : fractional flow reserve

FSU : formation sanitaire urbaine

HG : hôpital général

IDM : infarctus du myocarde

IDM ST+ : infarctus du myocarde avec sus-décalage persistant du segment ST

IDM ST- : infarctus du myocarde sans sus-décalage persistant du segment ST

IEC : inhibiteur de l'enzyme de conversion

IRM : imagerie par résonance magnétique

ISFC : International Society and Federation of Cardiology

LSR : limite supérieure de référence

MCV : maladies cardiovasculaires

MONICA: monitoring of trends and determinants in Cardiovascular disease.

NHLBI: National Heart, Lung, and Blood Institute.

NIMI : non ischemic myocardial injury

Nt pro-BNP : N-terminal pro-brain natriuretic peptide

OMS : organisation mondiale de la santé

OR : odds ratio

PAC : pontage aorto-coronarien

PRISMA : Preferred Reporting Items for Systematic Reviews and Meta-Analyses

REACTIV : Registre des infArctus de Côte d'Ivoire

RICO : obseRvatoire des Infarctus de la Côte d'Or

RR : risque relatif

SRIS : syndrome de réponse inflammatoire systémique

SWEDEHEART : Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery

Tnc : troponine cardiaque

Tnc US : troponine cardiaque ultrasensible

USIC : urgences et soins intensifs cardiologiques

VIH : virus de l'immuno-déficience humaine

WHF: world heart federation.

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1. Introduction

Les maladies cardiovasculaires (MCV) et notamment les cardiopathies ischémiques (CI) sont en progression constante dans le monde depuis 3 décennies, avec 274 nouveaux cas pour 100.000 habitants en 2019 ¹. Responsable de 16% des décès toutes causes confondues, elles représentent les premières causes de mortalité dans le monde ¹. Elles constituent aussi l'une des principales causes d'invalidité et de dégradation de la qualité de vie ²⁻⁴. Cependant, ces chiffres globaux masquent une réalité plus contrastée à l'échelle des différentes régions du monde. Sur le continent africain, si les CI ne figurent qu'à la 5^{ème} place des causes de décès derrière les affections néonatales et les maladies transmissibles, elles sont en pleine progression depuis 20 ans, liée en particulier à l'évolution des modes de vie ⁵. Ainsi, les CI représentent aujourd'hui le facteur principal de risque de décès chez les plus de 50 ans ⁶. En France, les MCV représentent la deuxième cause de décès, les CI et les infarctus du myocarde (IDM) étant les principaux responsables de la mortalité par MCV ².

L'IDM de type 2 est un type d'IDM plus récemment défini, largement sous diagnostiqué et pour lequel on manque encore de données épidémiologiques permettant de le comprendre, et d'appréhender ses enjeux pronostiques, afin de mieux le prendre en charge. C'est l'objet de ce travail de thèse. Au préalable, il est important de décrire les principaux mécanismes, le contexte épidémiologique, et les concepts diagnostiques qui ont abouti à la définition de ce type d'IDM.

Définition et classification des infarctus du myocarde

La physiopathologie de l'IDM correspond à la nécrose de cellules myocardiques due à une ischémie prolongée et irréversible. Depuis plus de 60 ans, le diagnostic d'IDM a été précisé, notamment en 2007 par les révisions successives de la définition universelle de l'IDM par la Société Européenne de Cardiologie (ESC) et les principales sociétés savantes internationales

dont l' American College of Cardiology (ACC) et l' American Heart Association (AHA) (Figure 1) ⁷⁻⁹. Sur la base de la quatrième définition universelle de l'IDM qui date de 2018 (la plus récente à ce jour), le diagnostic repose sur la détection d'une cinétique (élévation ou baisse) d'une Troponine cardiaque (Tnc) avec au moins une valeur supérieure au 99^{ème} percentile de la limite supérieure de la référence (LSR) associée à l'une des conditions suivantes : symptômes d'ischémie myocardique, nouvelles modifications électrocardiographiques (ECG), apparition d'ondes Q pathologiques, mise en évidence à l'imagerie d'une perte de viabilité myocardique ou d'anomalies récentes de la cinétique segmentaire dans un contexte clinique évocateur d'ischémie myocardique, ou identification d'un thrombus intra coronaire à la coronarographie ou après autopsie ⁹.

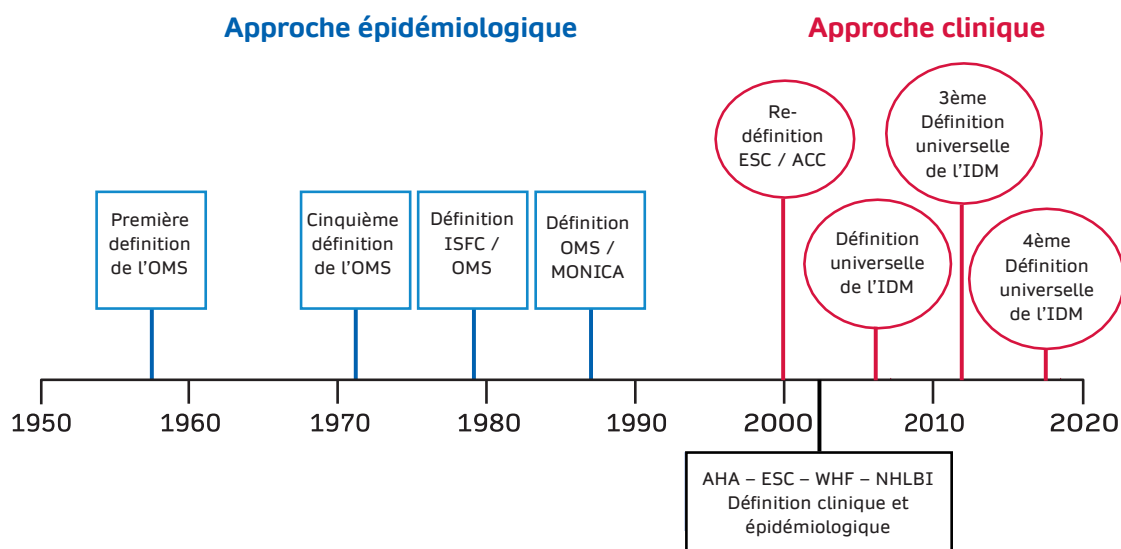


Figure 1 : Evolution des définitions universelles de l'infarctus du myocarde (adapté d'après Thygesen et al) ⁹

OMS : Organisation Mondiale de la Santé. ISFC : International Society and Federation of Cardiology. MONICA : MONIToring of trends and déterminants in Cardiovascular disease. ESC : European Society of Cardiology. ACC : American College of Cardiology. AHA : American Heart Association. IDM : infarctus du myocarde. WHF : World Heart Federation. NHLBI : National Heart, Lung, and Blood Institute.

En s'appuyant essentiellement sur ces concepts physiopathologiques, la quatrième définition universelle de l'IDM permet d'identifier cinq types d'IDM (types 1 à 5). Les différents types d'IDM sont présentés dans le Tableau 1.

Tableau 1 : Quatrième définition universelle de l'infarctus du myocarde (adapté de Byrne et al¹⁰ et Thygesen et al⁹)

Définition universelle de l'infarctus du myocarde	
<p>Une combinaison de critères est nécessaire pour poser le diagnostic d'infarctus aigu du myocarde, à savoir la détection d'une augmentation et/ou d'une diminution d'un biomarqueur cardiaque, de préférence la troponine cardiaque ultrasensible T ou I, avec au moins une valeur supérieure au 99e percentile de la limite supérieure de référence et au moins l'un des éléments suivants :</p> <ul style="list-style-type: none"> (i) Symptômes d'ischémie myocardique (ii) Nouvelles modifications ECG (iii) Apparition d'ondes Q pathologiques à l'ECG (iv) Mise en évidence à l'imagerie d'une perte de viabilité myocardique ou d'anomalies récentes de la cinétique segmentaire dans un contexte clinique évocateur d'ischémie myocardique (v) Thrombus intra coronaire visualisé à l'angiographie ou après autopsie 	
Différents types d'infarctus du myocarde décrits sur la base des différentes conditions pathologiques sous-jacentes	
IDM de type 1	Rupture de plaque, ulcération, fissure ou érosion à l'origine d'un thrombus dans une ou plusieurs artères coronaires, aboutissant à une diminution du débit sanguin coronaire et/ou à des embolisations distales et une nécrose myocardique
IDM de type 2	Nécrose myocardique dans laquelle une condition autre qu'une plaque coronaire instable provoque un déséquilibre apport/besoin en oxygène du myocarde. Ces mécanismes incluent : hypotension, hypertension, tachyarythmie, bradyarythmie, anémie, hypoxémie, sapsme coronaire, embolie coronaire et dysfonction microvasculaire
IDM de type 3	IDM entraînant un décès d'origine cardiaque avec des symptômes évocateurs d'une ischémie myocardique en l'absence de biomarqueurs ou IDM détecté à l'autopsie
IDM de type 4	IDM dû à une intervention coronarienne percutanée
IDM de type 5	IDM dû à un pontage aorto-coronarien.

ECG : électrocardiogramme. IDM : infarctus du myocarde.

L'IDM résultant d'une athéro-thrombose coronaire due à rupture, une ulcération, une fissuration ou une érosion d'une plaque d'athérome désigne l'IDM de type 1, le plus classiquement décrit. La rupture de plaque peut se compliquer non seulement d'une thrombose intraluminale, mais aussi d'une hémorragie intraplaque ¹¹. Il s'agit du type le plus fréquent d'IDM, dont la prise en charge est dépendante notamment du délai entre l'apparition des symptômes et le diagnostic. Elle repose également sur les anomalies ECG permettant de le classement en IDM avec sus-décalage persistant du segment ST (IDM ST+) ¹², ou sans sus-décalage persistant du segment ST (IDM ST-T+) ¹³. La stratégie thérapeutique, qui est adaptée à ces différentes situations, a fait l'objet de recommandations récemment actualisées par l'ESC en 2023 ¹⁰. L'approche invasive (avec coronarographie en vue d'une angioplastie) est la plus précoce possible dans les IDM ST+, alors que dans les IDM ST-, elle dépend de la stratification du risque ischémique du patient, en fonction des paramètres cliniques, ECG et biologiques.

Outre l'IDM de type 1, la définition universelle identifie également les IDM de type 3 à 5. Ainsi, un décès d'origine cardiaque chez les patients ayant présentant des symptômes évocateurs d'ischémie myocardique, avec de nouvelles modifications ischémiques sur l'ECG ou une fibrillation ventriculaire, avant que les biomarqueurs de nécrose myocardique n'aient pu être dosés ou avant la détection d'une cinétique de ces biomarqueurs, répondent aux critères de l'IDM type 3, en plus des patients chez qui l'IDM a été confirmé par autopsie. L'IDM de type 4 correspond aux IDM survenant après une angioplastie coronaire transluminale (ATL) (4a : ≤ 48 heures après la procédure, 4b : thrombose aiguë de stent, 4c : resténose intra stent). L'IDM lié à la réalisation d'un pontage aorto-coronaire (PAC) est appelé IDM de type 5. Ces autres types d'IDM (Types 3, 4, 5) dont 2 sont essentiellement d'origine iatrogène, ne font pas partie de ce travail de thèse.

Troponines, lésions myocardiques, et IDM type 2

Dans ce cadre, l'IDM de type 2 est défini par une nécrose myocardique dans laquelle une condition autre qu'un processus d'athéro-thrombotique provoque un déséquilibre entre les apports et les besoins en oxygène du myocarde. Cette définition par défaut repose donc sur la détection d'une nécrose myocardique. Depuis plus de 10 ans, le dosage des biomarqueurs de nécrose myocardique, et spécifiquement la TnIc ou TnTc représente aujourd'hui l'un des critères principaux du diagnostic d'IDM. La TnIc et la TnTc ont supplanté les autres marqueurs dont la Creatine Kinase Myocardial Band (CK-MB) du fait de leur très forte spécificité myocardique ¹⁴. Aujourd'hui, le dosage des Tnc ultrasensibles (Tnc US) constitue la référence en pratique clinique, à cause de leur faible taux d'imprécision à la LSR au 99^e percentile (ou coefficient de variation maximal), qui est inférieur à 10%, et la possibilité de les quantifier chez au moins 50% des individus en bonne santé ¹⁵. Leur dosage permet ainsi de détecter des concentrations 10 fois plus faibles qu'avec les précédentes méthodes, offrant ainsi une meilleure sensibilité. Il a été montré que l'utilisation des Tnc US augmentait d'un facteur 2 la détection des IDM type 2 ¹⁴.

La détection d'une élévation du taux de Tnc au-delà du 99^e percentile de LSR définit la présence d'une lésion myocardique ⁹, qui peut être considérée comme aigüe ou chronique respectivement selon qu'il existe une cinétique (augmentation et/ou baisse) ou non des valeurs de Tnc. C'est une lésion myocardique survenant dans un contexte clinique évocateur d'ischémie myocardique aigüe, qui permet de poser le diagnostic d'IDM ⁹ (Figure 2).

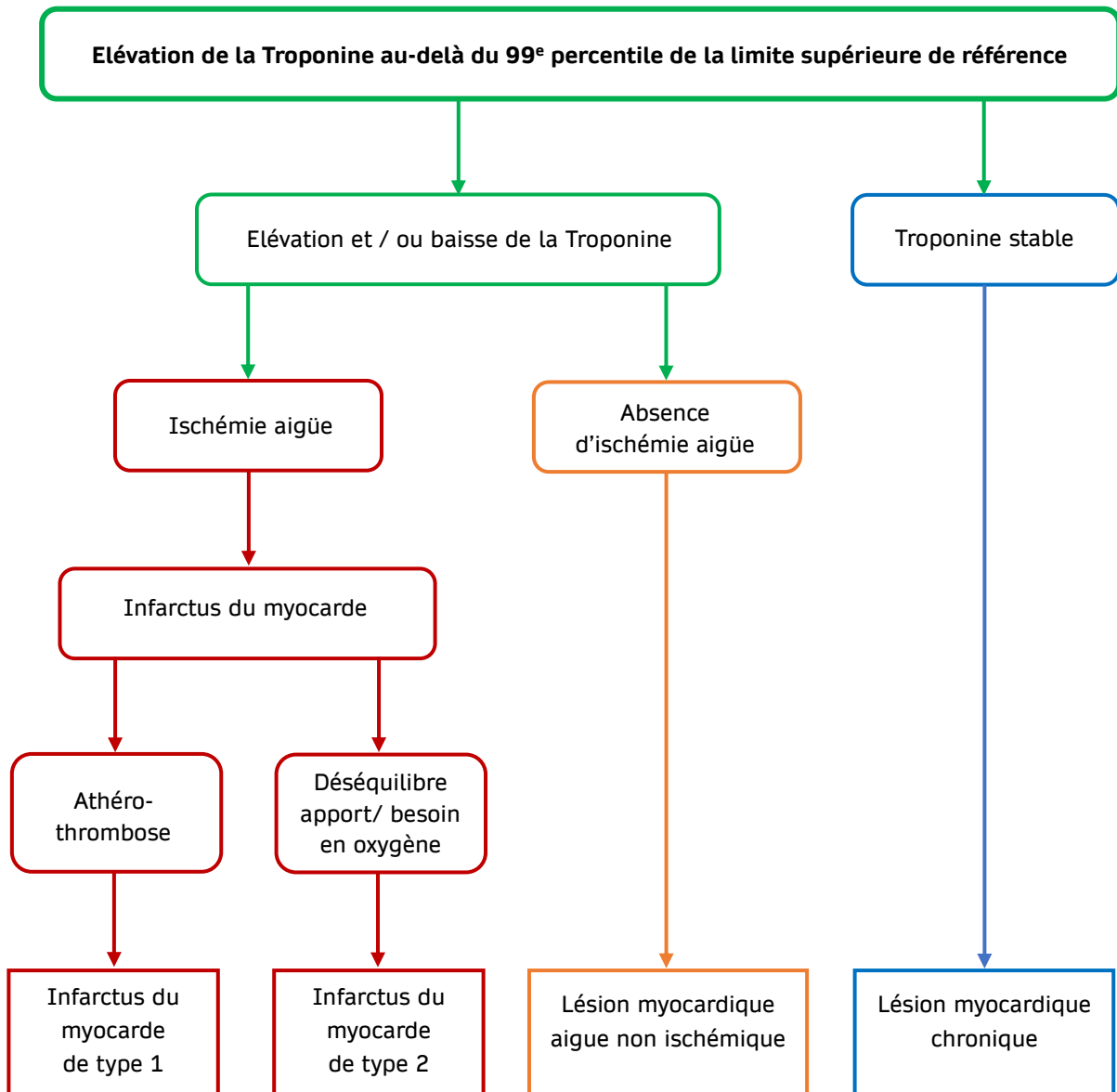


Figure 2 : Modèle d'interprétation des lésions myocardiques (adapté d'après Thygesen et al⁹)

Les causes de lésions myocardiques aigües ischémiques sont donc multiples, et elles vont conduire à un IDM de type 2 lorsqu'elles sont consécutives à un déséquilibre entre les apports et les besoins en oxygène du tissu myocardique. Elles peuvent donc correspondre à une réduction des apports d'oxygène au myocarde, ou une augmentation des besoins, situations qui peuvent co-exister entre elles.

Les lésions myocardiques survenant en dehors de tout contexte clinique évocateur d'ischémie myocardique aiguë sont regroupées sous le terme lésions myocardiques non ischémiques (*non-ischemic myocardial injury ou NIMI*)^{9,16,17}. Les différentes conditions ischémiques et non ischémiques de lésions myocardiques associées à l'IDM de type 2 ou aux NIMI sont décrites dans le Tableau 2.

Tableau 2 : Conditions associées à une lésion myocardique, en dehors de l'infarctus de type 1 (infarctus de type 2 et NIMI) (adapté d'après Byrne et al ¹⁰)

Lésion myocardique lié à une ischémie myocardique aiguë due à un déséquilibre apport/besoin en oxygène (Infarctus du myocarde de type 2)
Diminution de la perfusion myocardique
<ul style="list-style-type: none"> • Vasospasme coronaire, dysfonction microvasculaire • Embolie coronaire • Dissection coronaire non athéromateuse • Bradycardie soutenue • Hypotension artérielle ou choc • Insuffisance respiratoire • Anémie sévère
Augmentation de la demande en oxygène
<ul style="list-style-type: none"> • Tachycardie soutenue • Hypertension artérielle sévère avec ou sans hypertrophie ventriculaire gauche
Autres causes de lésions myocardiques
Causes cardiaques
<ul style="list-style-type: none"> • Insuffisance cardiaque • Myocardite • Cardiomyopathies (tous types) • Syndrome de Tako-Tsubo • Contusion cardiaque ou procédures cardiaques (pontage aorto-coronarien, angioplastie coronaire, ablation, stimulation cardiaque, cardioversion ou biopsie endomyocardique)
Causes systémiques
<ul style="list-style-type: none"> • Sepsis, pathologie infectieuse • Insuffisance rénale chronique • Accident vasculaire cérébral, hémorragie méningée • Embolie pulmonaire, hypertension pulmonaire • Pathologies infiltratives (ex : amylose, sarcoïdose, hémochromatose, sclérodermie) • Toxicité myocardique médicamenteuse ou empoisonnement (ex : doxorubicine, 5-fluorouracil, trastuzumab, venin de serpent) • Patients en état critique • Exercice physique intense • Rhabdomyolyse

NIMI : lésions myocardiques non ischémiques.

L'IDM de type 2, un paradigme encore flou

Une entité physiopathologique hétérogène

Ainsi, l'IDM de type 2 correspond à des conditions particulièrement hétérogènes qui associent, en plus des critères de l'IDM, des conditions pathologiques à l'origine d'un déséquilibre entre les apports et les besoins en oxygène du myocarde, et en l'absence d'athéro-thrombose. Afin d'améliorer la compréhension des mécanismes sous-jacents, des travaux de notre groupe, inspirés de l'approche gériatrique (modèle de Bouchon), ont proposé que l'IDM de type 2 résulte de la convergence de trois facteurs interdépendants : 1) le vieillissement vasculaire, y compris l'athérosclérose 2) les conditions prédisposantes cardiaques et extracardiaques chroniques et 3) les déclencheurs ischémiques (ou facteurs précipitants) ^{18,19} (Figure 3).

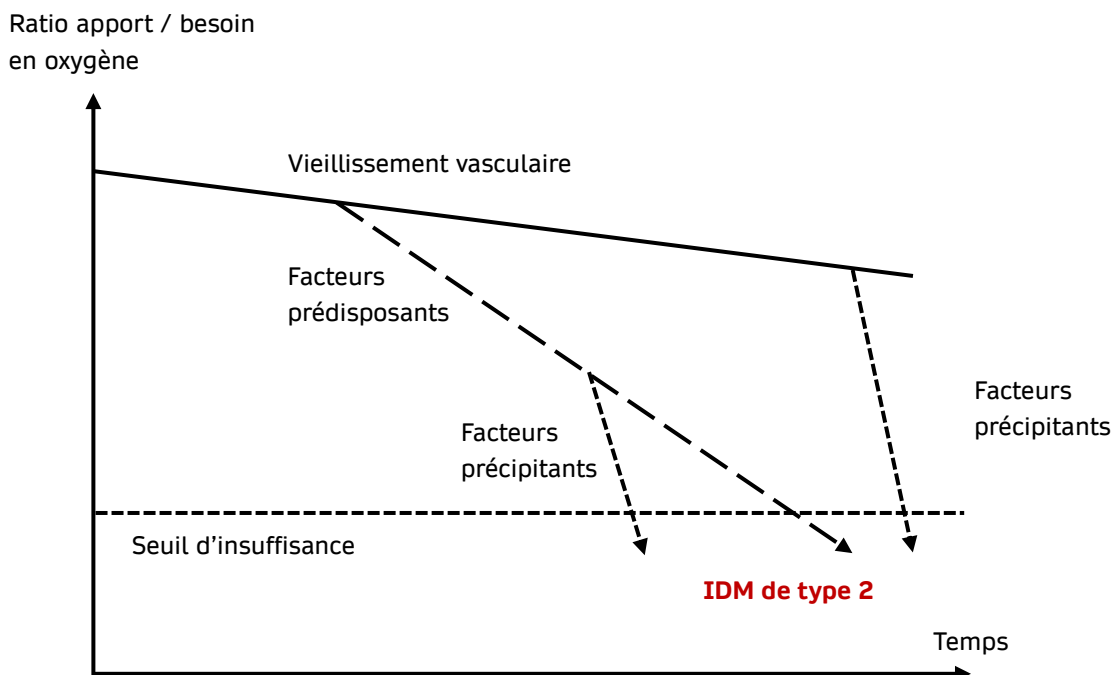


Figure 3 : Physiopathologie de l'IDM de type 2 (adapté d'après Bouchon JP¹⁹)

IDM : infarctus du myocarde.

Des critères diagnostiques qui restent à définir

Des critères standards ont été proposés pour définir les situations de déséquilibre apports/besoins en oxygène permettant de retenir un IDM de type 2^{8,20-24} afin de garantir une uniformité diagnostique pour tous les praticiens, et permettre une reproductibilité des résultats à l'échelle d'autres études. Cependant l'utilisation en pratique clinique de valeurs précises est de pertinence discutable, car il n'existe pas de consensus à l'heure actuelle sur les critères diagnostiques. Les études portant sur les IDM de type 2 ont le plus souvent utilisé des critères empiriques, issus de la pratique clinique, pour retenir les situations d'inadéquation apports/besoins en oxygène potentiellement pourvoyeuses d'ischémie myocardique. De plus, les limites pour définir ces facteurs précipitants ischémiques peuvent varier considérablement d'un patient à l'autre en fonction de l'importance du facteur déclenchant, de la présence de comorbidités, de la sévérité de la maladie coronarienne sous-jacente et des anomalies structurales cardiaques éventuelles⁹. Dans le contexte de l'IDM de type 2, des mécanismes hétérogènes entraînant un déséquilibre en apport/besoin en oxygène du myocarde, et des facteurs déclenchants non coronariens peuvent conduire à une ischémie myocardique, modulée par la présence et la gravité de la maladie coronarienne sous-jacente. Ainsi, les patients présentant un IDM de type 2 et une coronaropathie plus sévère ont probablement un seuil ischémique inférieur à celui des patients sans coronaropathie. Il a été suggéré que les patients présentant une coronaropathie plus étendue présentent des lésions myocardiques plus importantes et donc des taux de Tnc plus élevés^{9,25}. Les données de l'Observatoire des Infarctus de Côte d'Or (RICO) ont montré que l'anémie et le rétrécissement aortique représentaient des facteurs pré-disposants majeurs, tandis que les infections, notamment respiratoires, étaient les principaux facteurs précipitants, devant les tachyarythmies, l'insuffisance cardiaque aigüe et le spasme coronaire. Ce concept d'infection concomitante à l'IDM a été précisé par notre groupe²⁶ et il a été montré que l'incidence de l'IDM type 2 était presque aussi fréquente que celle de

l'IDM type 1 parmi les personnes vivant avec le virus de l'immuno-déficience humaine (VIH) et recevant des soins aux États-Unis ²⁷. Les principaux facteurs (prédisposants et précipitants) sont présentés sur la Figure 4.

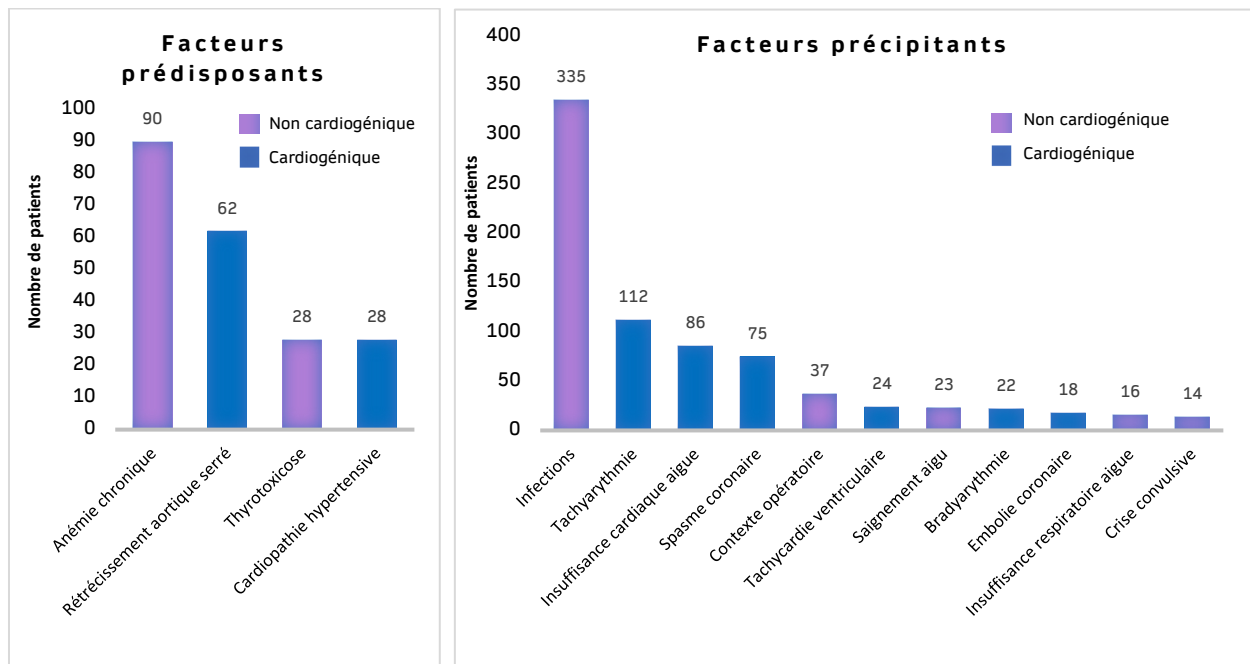


Figure 4 : Facteurs prédisposants et précipitants des infarctus de type 2 (d'après Putot et al ²⁸).

L'imagerie coronaire, une aide au diagnostic différentiel des IDM type 2 ?

Sur la base de la définition universelle de l'IDM, la coronarographie n'est pas indispensable pour le diagnostic des IDM de type 2, mais elle peut aider à la différenciation entre IDM de type 1 et IDM de type 2 en montrant l'absence d'athéro-thrombose, dont la présence définit l'IDM de type 1. Cependant, en l'absence d'imagerie endocoronaire (tomographie par cohérence optique ou échographie), il peut être parfois difficile de confirmer de façon formelle la présence d'une plaque instable. Il faut aussi préciser qu'une rupture de plaque n'est pas spécifique aux IDM de type 1, car elle peut être retrouvée en dehors d'un contexte de syndrome coronarien aigu, chez des sujets souffrant d'angor, et même chez des coronariens stables ²⁹.

La coronarographie reste peu réalisée parmi les patients atteints d'IDM de type 2, entre 5 et 60% des cas selon les séries³⁰. Une étude américaine récente portant sur 268 850 patients admis pour IDM de type 2 a montré que la coronarographie n'a été pratiquée que chez 11,2% d'entre eux³¹. Dans une méta analyse récente³² portant sur 40 études et ayant inclus 98 930 patients (dont 13 803 avec IDM de type 2), la coronarographie n'a été réalisée que chez 34,1% des patients atteints d'IDM de type 2, contre 85,5% dans l'IDM de type 1, et retrouvait une maladie coronaire obstructive dans 34% des cas. Les critères angiographiques pour définir une maladie coronaire obstructive dans ces études étaient très variables, et certains registres ont démontrés qu'une maladie coronaire obstructive étaient plus fréquemment associée à l'IDM de type 2 (entre 57 et 61%), en considérant les sténoses à partir de 50%^{33,34}.

D'autres modalités d'imagerie peuvent présenter une utilité diagnostique, en particulier l'imagerie par résonance magnétique (IRM) cardiaque et le scanner coronaire. Dans une étude prospective³⁵ parmi 100 patients avec un diagnostic initial d'IDM de type 2, une imagerie coronaire invasive (coronarographie) ou non invasive (scanner cardiaque) couplée à une imagerie cardiaque non invasive (IRM ou échographie cardiaque) permettait de reclasser 7 patients : 4 avec IDM de type 1, 1 avec IDM de type 4b and 2 avec *NIMI*. Plus récemment, le scanner coronaire a été évalué dans l'étude prospective DEFINing the PrEvalence and Characteristics of Coronary Artery Disease Among Patients With TYPE 2 Myocardial Infarction Using CT-FFR (DEFINE TYPE 2 MI), qui a inclus 50 participants³⁶. Une coronaropathie obstructive était retrouvée chez 42% des patients, en considérant des sténoses \geq 50%³⁶. De plus, il a été montré en imagerie coronaire non invasive (coro-scanner) que l'étendue des plaques d'athérome à faible atténuation, reflets de la présence d'un cœur nécrotique au sein des plaques d'athérome, était significativement plus importante dans les IDM de type 1 que dans les type 2, avec une forte valeur prédictive même après ajustement à la sévérité de l'atteinte coronaire et aux caractéristiques cliniques (Odds ratio (OR) : 3,44 ; intervalle de confiance à

95% (IC95%) 1,84 - 6,95 ; $p < 0,001$)³⁷. L'analyse de la composition des plaques en imagerie coronaire pourrait ainsi aider au diagnostic différentiel de ces 2 types d'IDM.

Si la maladie coronaire est fréquente dans l'IDM de type 2, ses différentes interactions avec les facteurs précipitants ischémiques et son impact à court et à long terme sont très peu documentés^{34,38,39}. Elle est de plus en plus considérée comme un élément déterminant dans la physiopathologie des IDM de type 2, susceptible d'améliorer la compréhension de cette entité souvent considérée comme énigmatique⁴⁰.

De multiples facteurs de variation de l'épidémiologie des IDM de type 2

L'épidémiologie des IDM type 2, est le plus souvent limitée aux populations nord-américaines ou européennes. Elle indique que les patients atteints d'IDM de type 2 sont plus âgés (avec une différence d'environ 6 ans) et présentent davantage de comorbidités que les patients atteints d'IDM de type 1^{32,41}. Ainsi, les patients avec un IDM de type 2, souffrent 3 fois plus fréquemment d'une insuffisance rénale (22,8% vs 17,3%; OR = 1,87 ; IC95% 1,53-2,28), d'une insuffisance cardiaque chronique (13,1% vs 7,6%; OR = 2,35 ; IC95% 1,82-3,03) et de fibrillation atriale (22,9% vs 6,1%; OR = 3,02 ; IC95% 2,29-3,99)³². Les données disponibles suggèrent que le taux de femmes parmi les patients présentant un IDM de type 2 est élevé, aux alentours de 50%^{30,32}. Il n'existe que peu de données épidémiologiques du type 2 sur les populations africaines, qui ont pourtant des spécificités en terme de démographie, facteurs de risque et de prise en charge^{42,43}. En effet, notre groupe a été un des premiers à mettre en évidence les caractéristiques des IDM dans ces populations⁴². A partir d'une revue systématique de 27 études, nous avons montré que les patients d'Afrique sub-Saharienne hospitalisés pour un IDM sont globalement plus jeunes (âge moyen entre 55 et 57 ans,) que ceux des pays occidentaux, avec quelques divergences dans certaines études. La mortalité hospitalière est élevée, probablement en lien avec les longs délais d'admission et le faible taux de patients bénéficiant des procédures de reperfusion en phase aigue⁴². Cependant, à ce jour,

la prévalence et le profil épidémiologique des patients présentant un IDM de type 2 en Afrique Sub-Saharienne n'a pas encore été décrit. C'est pourquoi nous nous attacherons à l'étudier.

Les études de cohorte réalisées dans les pays développés montrent que les patients atteints de d'IDM de type 2 présentent un pronostic à court et à long terme défavorables ^{30,32} comparativement aux IDM de type 1. Les patients atteints d'IDM de type 2 ont une mortalité toutes causes significativement plus élevée que les patients atteints d'IDM de type 1 : deux fois plus importante en intra-hospitalier (12,5% vs 5,8%), trois fois plus importante à 1 an (18,9% vs 5,4%) et à plus long terme entre 5–10 ans (53,7% vs 28,5%) ³². Il semble également que l'IDM de type 2 soit associé à une mortalité cardiovasculaire (CV) plus importante, presque trois fois plus élevée dans certaines études ⁴⁴.

En plus de l'hétérogénéité de la définition des facteurs contributifs aux IDM type 2, d'autres variables influencent également l'épidémiologie de ce type d'IDM. La plupart de ces études sur l'IDM de type 2 ont inclus des patients hospitalisés dans des services de cardiologie, en particulier en unité de soins intensifs cardiologiques (USIC). En réalité, une proportion considérable de patients admis pour IDM de type 2 est prise en charge en dehors des services de cardiologie, comme la gériatrie ou les services d'urgences ^{45,46}, conduisant à des caractéristiques épidémiologiques particulièrement hétérogènes. Il a ainsi été montré que parmi les patients hospitalisés pour une souffrance myocardique aiguë (IDM out NIMI) en dehors des services de cardiologie, 31,9% étaient représentés par les IDM de type 2, alors que seulement 15,9% des patients hospitalisés pour IDM dans un service de cardiologie présentaient un IDM de type 2 ⁴⁵. Les patients pris en charge en dehors des services de cardiologie sont plus âgés, avec davantage de comorbidités (notamment une insuffisance rénale, une insuffisance cardiaque, et une maladie respiratoire chronique). La mortalité est plus élevée en milieu non cardiologique, après ajustement aux facteurs de risque, à l'index de Charlson, et aux données cliniques et paracliniques, que ce soit à 30 jours (Risque Relatif (RR) 2,28[1,62–3,22]), à 1 an

(RR 1.82[1.39–2.36]) et jusqu'à 5 ans (RR = 1,62[1,32–1,98]). Cette surmortalité ne semble pas influencée par les thérapeutiques hospitalières, en particulier l'angioplastie coronaire.⁴⁵

Afin de mieux cerner les IDM type 2, une redéfinition des IDM de type 1 et 2 a été proposée par de Lemos et al⁴⁷ en 2019. Dans cette nouvelle classification, les auteurs ont d'abord proposé de reconsidérer certains sous-types d'IDM de type 2 (dissection spontanée de l'artère coronaire, embolie coronaire et anomalies vasomotrices (vasospasme et dysfonction microvasculaire)) comme des IDM de type 1. Tous les phénomènes intra-coronariens se retrouvent ainsi dans le même groupe, et ils ont pour point commun la nécessité de la coronarographie dans le diagnostic de ces entités pathologiques, et parfois le recours à l'ATL dans certaines situations, comme dans les IDM de type 1 de la quatrième définition universelle. Deuxièmement, les auteurs proposent de catégoriser les IDM de type 2 selon la présence ou l'absence d'une coronaropathie obstructive (sténose $\geq 50\%$ dans au moins un vaisseau coronaire). Cependant cette reclassification nécessite d'être évaluée afin d'en apprécier à large échelle l'impact diagnostique et pronostique. C'est pourquoi nous l'avons analysée au cours de ce travail.

Compte tenu de ces nombreuses incertitudes, notamment diagnostiques, ce travail de thèse a comme objectifs de préciser les aspects épidémiologiques et diagnostiques encore mal connus concernant l'IDM de type 2, notamment la place de la maladie coronaire, et à évaluer la pertinence clinique et pronostique de la proposition de nouvelle classification. Il s'appuiera principalement sur la base de données du RICO. Il s'agit d'un Observatoire de la prise en charge des IDM au niveau du département de la Côte d'Or, qui permet de recueillir depuis 2001 et de traiter les informations épidémiologiques nécessaires à l'étude des caractéristiques des patients, de leurs facteurs de risque, de leur prise en charge et leur pronostic. Au 31/12/2020, plus de 18 000 patients ont été inclus dans cette base de données unique en France. Après un travail préalable d'adjudication des cas et des étiologies, selon les critères validés par les travaux

notamment issus de notre groupe ^{28,39,48}, il s'attachera à identifier le pronostic de ces nouveaux sous-types. De plus, afin de mieux comprendre le rôle de la maladie coronaire dans les IDM de type 2, nous avons effectué une revue systématique de la littérature permettant de donner une approche synthétique de cette problématique. Enfin, nous avons utilisé les données du REgistre des InfArctus de CÔTe d'IVOire (REACTIV) de l'Institut de cardiologie d'Abidjan, centre public de référence pour la prise en charge des MCV en Côte d'Ivoire, afin d'identifier les spécificités des IDM de type 2 dans cette population.

2. Méthodologie générale

Ce travail a été réalisé principalement à partir des données de la base RICO, observatoire multicentrique qui recueille de manière prospective les données de tous les patients consécutifs âgés de 18 ans, hospitalisés pour un IDM aigu dans les 6 centres hospitaliers ou clinique du département de la Côte d'Or depuis 2001⁴⁹. Pour la présente étude, les patients hospitalisés pour un IDM entre 2012 et 2017 ont été inclus. L'IDM a été retenu selon la définition universelle de l'IDM en vigueur⁹, incluant la différenciation entre les IDM de type 1 et de type 2. L'adjudication en IDM de type 1 ou de type 2 a été réalisée de façon rétrospective par des investigateurs indépendants expérimentés (YC, HY et AP). Les critères standards pour retenir le diagnostic d'IDM de type 2 sont ceux habituellement utilisés dans la littérature^{8,20-24}. Les divergences ont été résolues par consensus, après un ré-examen approfondi des dossiers médicaux. En cas de désaccord persistant, la décision a été prise par un autre cardiologue indépendant. Les IDM de type 3, 4 et 5 n'ont pas été inclus. Nous avons ensuite identifié comme IDM de type 1 certains sous-groupes d'IDM initialement classés de type 2 (dissection coronaire spontanée, spasme coronaire, embolie coronaire) selon la nouvelle classification proposée par de Lemos⁴⁷, et réparti les IDM de type 2 selon la présence ou l'absence de coronaropathie obstructive sous-jacente:

- Type 1 :
 - Type 1A : athérombose
 - Type 1B : dissection coronaire spontanée
 - Type 1C : embolie coronaire
 - Type 1D : spasme coronaire / anomalies microvasculaires
- Type 2
 - Type 2A : présence d'une coronaropathie obstructive

- Type 2B : absence de coronaropathie obstructive

Pour chaque patient, nous avons recueilli les variables démographiques, les facteurs de risque et antécédents CV, de même que les données cliniques, comme décrit précédemment ⁴⁹. Les données ECG, échocardiographiques et biologiques ont été précisées à l'admission ou au cours de l'hospitalisation. La coronarographie et l'ATL ont été réalisées selon les pratiques locales, et conformément aux recommandations pour la période considérée ^{10,12,13}. Les lésions coronaires obstructives étaient définies par une sténose coronaire $\geq 50\%$, et la sévérité des lésions était appréciée par le score *SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery* (SYNTAX) ⁵⁰. Les événements survenus à l'hôpital après l'admission à l'USIC ont été enregistrés, notamment les événements CV graves et le décès (d'origine CV et toutes causes confondues), de même que les décès à un an. L'analyse statistique a consisté à comparer les variables qualitatives et quantitatives et à déterminer le niveau d'agrément pour l'adjudication en IDM de type 1 et de type 2 par les deux investigateurs. Nous avons réalisé une analyse de survie, avec les courbes de Kaplan Meier pour la mortalité à 1 an (d'origine CV et toutes causes), et une analyse de régression de Cox multivariée pour identifier les facteurs prédictifs de mortalité.

Nous avons également réalisé une revue systématique de toutes les études en langue anglaise ayant évalué la maladie coronaire dans l'IDM de type 2, publiées depuis la parution de sa définition, soit entre 2012 and 2022, à partir de la base de données MEDLINE (PubMed; National Library of Medicine, National Institutes of Health, Bethesda, United States of America). Ce travail a été réalisé conformément aux critères *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) pour les revues systématiques ⁵¹. Ces études devaient concerner la prévalence, le diagnostic, l'impact pronostique ou les stratégies thérapeutiques en présence d'une maladie coronaire obstructive dans l'IDM de type 2, avec les termes correspondant.

Enfin, nous avons travaillé sur les données du registre REACTIV. Il s'agit d'un registre mono-centrique qui recueille de manière prospective des données sur tous les patients consécutifs âgés de plus de 18 ans, hospitalisés pour un IDM dans l'USIC de l'Institut de cardiologie d'Abidjan depuis 2010⁴³. Pour cette étude, tous les patients atteints d'IDM entre 2018 et 2022 et chez qui une coronarographie a été réalisée dans le cadre de l'IDM ont été inclus. Le recueil des variables s'est fait conformément à celui du RICO dans le cadre de cette étude. L'analyse statistique a consisté à comparer les variables qualitatives et quantitatives et à déterminer le niveau d'accord concernant l'adjudication en IDM de type 1 et de type 2 par deux cardiologues indépendants.

3. Approche épidémiologique et pronostique des infarctus de type 2

Ce travail s'est donc intéressé à préciser les données épidémiologiques et à mieux comprendre l'impact pronostique de la présence d'une maladie coronaire obstructive chez les patients présentant un IDM de type 2.

3.1. Evaluation de l'impact d'une reclassification des infarctus du myocarde de type 2

La nouvelle classification de l'IDM proposée par de Lemos et al ⁴⁷ repose sur 1) le transfert de certains sous-types d'IDM de type 2 (dissection spontanée de l'artère coronaire, embolie coronaire et anomalies vasomotrices) vers les IDM de type 1, et 2) la division des IDM de type 2 en 2 sous-groupes selon la présence (IDM de type 2A) ou l'absence (IDM de type 2B) d'une coronaropathie obstructive. C'est cette deuxième proposition qui constitue l'élément marquant de cette nouvelle classification. En effet dans l'IDM de type 2, les enjeux pronostiques liés à la présence d'une maladie coronaire significative ont été très peu étudiés ^{34,38,39}. A partir de la base de données RICO, ces travaux visaient à décrire la prévalence et les caractéristiques des IDM de type 2A et 2B, ainsi que des IDM de type 1A (par athérombose) qui représentaient le principal sous-groupe des IDM de type 1. De plus, nous avons évalué l'impact pronostique de la maladie coronaire dans les IDM de type 2 au suivi à 1 an. Nous avons également précisé les différents facteurs déclenchants des IDM de type 2 selon la présence ou l'absence de maladie coronaire obstructive.

Ces travaux ont été publiés dans *American Heart Journal* en 2023.

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Diagnostic and prognostic impact of new pathophysiology-based categorization of type 1 and type 2 myocardial infarction: data from the French RICO survey

Hermann YAO^{1,2,3}, MD, MPH, Yves COTTIN¹, MD, PhD, Frédéric CHAGUE¹, MD, Maud MAZA¹, Msc, Florence BICHAT¹, PhD, Marianne ZELLER^{1,2}, PhD, Alain PUTOT², MD, PhD.

¹ Cardiology department, University Hospital Center Dijon Bourgogne, Dijon, France

² PEC2, EA 7460, UFR Health Sciences, University of Bourgogne Franche Comté, Dijon, France

³ Abidjan Heart Institute, Côte d'Ivoire

Corresponding author:

Hermann Yao

PEC2, EA 7460, UFR Health Sciences,

University of Bourgogne Franche Comté, Dijon, France

hermannyao@gmail.com

Declarations of interest

None

Abstract

Background: A new classification of type 1 and 2 myocardial infarction (MI) derived from the 4th universal definition of MI (UDMI) has been recently proposed, based on pathophysiology of coronary artery disease (CAD). We assessed the impact of this new MI categorization on epidemiology and outcomes, considering type 1 MI and type 2 MI, with and without CAD.

Methods: Retrospective study including all consecutive patients hospitalized for an acute MI in a multicenter database (RICO). MI was defined according to current UDMI. Rates and outcomes of T1MI and T2MI were addressed according to the new classification.

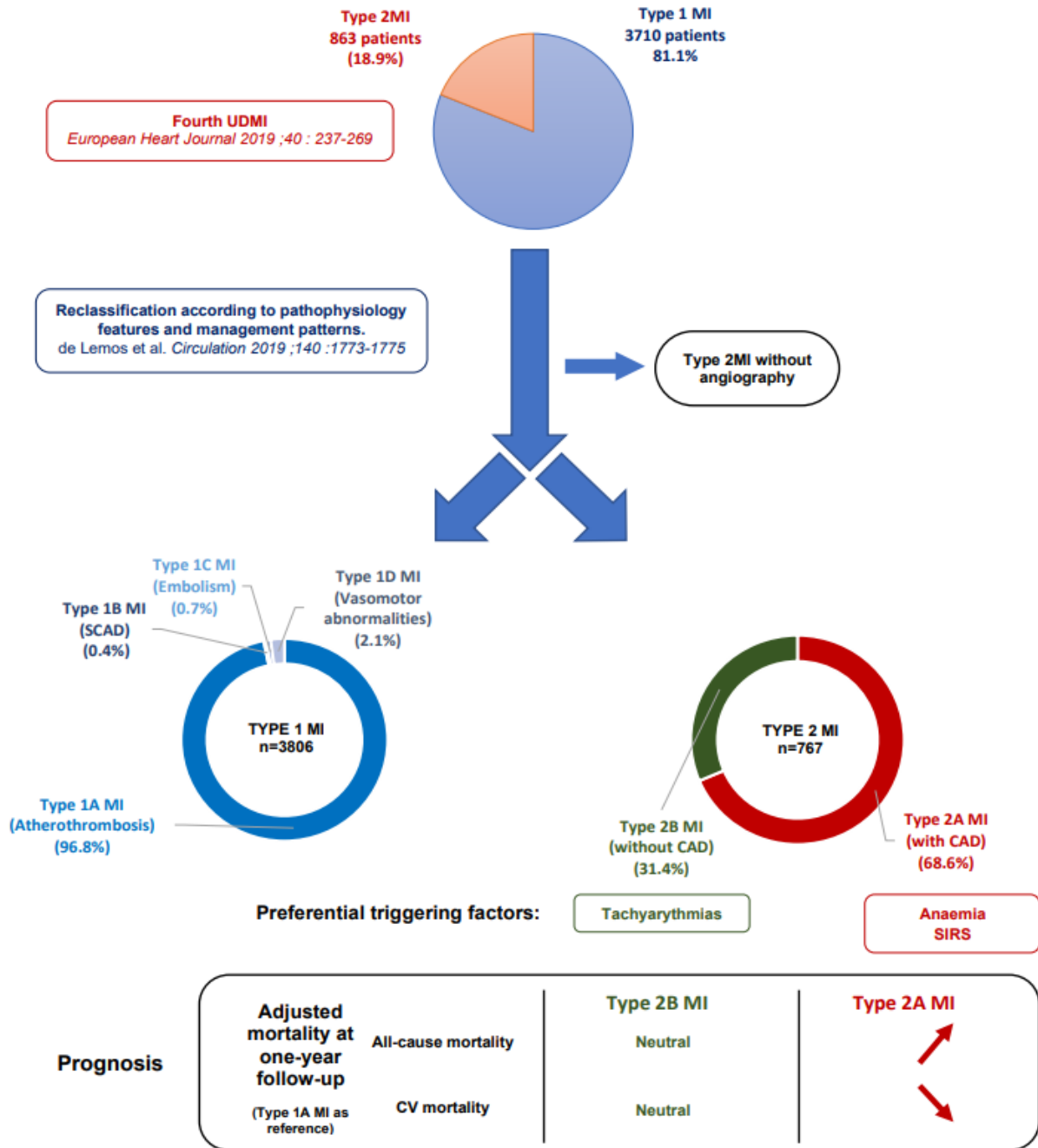
Results: Among the 4573 patients included in our study, 3710 patients (81.1%) were initially diagnosed with T1MI and 863 (18.9%) with T2MI. After reclassification, 96 T2MI patients were moved into the T1MI category. Out of the remaining 767 patients with T2MI, 567 underwent coronary angiography, and were adjudicated as type 2A MI (68.6%) with obstructive CAD, and type 2B MI (31.4%) without obstructive CAD.

When compared with T1MI and T2BMI, T2AMI patients had worse in-hospital outcomes, including severe heart failure ($p < 0.001$), atrial fibrillation or flutter ($p < 0.001$) and severe bleeding ($p < 0.001$). Kaplan-Meier one-year survival curves showed higher all-cause and CV causes mortality in T2AMI patients compared to T1MI and T2BMI ($p < 0.001$). In multivariate Cox regression analysis, type of MI was independent predictor of death.

Conclusion: Our large observational multicenter study shows major disparities in mortality according to type of MI and support the relevance of the new MI classification to improve risk classification, taking into account CAD in T2MI. Our findings may help identifying specific phenotypes and considering personalized diagnostic and management strategies.

Key words: Type 1 myocardial infarction; Type 2 myocardial infarction; Coronary artery disease; Prognosis.

Graphical Abstract



Introduction

The pathophysiology of myocardial infarction (MI) refers to irreversible myocardial ischemia resulting in myocardial cells death. The most common type of MI, type 1 MI (T1MI), is defined as MI due to atherothrombotic coronary artery disease (CAD), and usually released by atherosclerotic plaque disruption (or rupture or erosion). By contrast, MI secondary to mismatch of myocardial oxygen supply/demand is defined as type 2 MI (T2MI) [1]. Clinical classification of T2MI was introduced in 2007², and revised last time in the 4th universal definition of MI (UDMI) in 2018 [1]. However, although largely prevalent, T2MI diagnosis remains confusing, with significant uncertainty on how to characterize and manage this heterogeneous group of patients.

By 2019, a redefinition of T1MI and T2MI has been proposed by de Lemos JA et al [3], considering the pathophysiological and diagnostic features, and management patterns on some underlying mechanisms of T2MI that border with T1MI. T1MI was proposed to be divided into 4 subgroups: type 1A (T1AMI): plaque disruption/erosion, type 1B (T1BMI): spontaneous coronary artery dissection (SCAD), type 1C (T1CMI): coronary embolism, type 1D (T1DMI): vasomotor abnormalities including vasospasm or microvascular dysfunction. SCAD, coronary embolism and vasomotor abnormalities were previously classified as T2MI. T2MI, as a heterogeneous group of acute coronary events, were proposed to be categorized into 2 groups based on the presence (or not) of CAD, i.e. type 2A (T2AMI): presence of obstructive CAD (defined as $\geq 50\%$ coronary stenosis) and type 2B (T2BMI): absence of obstructive CAD [3]. Ischemic triggers already identified in the pathophysiology of T2MI and diagnosed based upon clinical criteria at the time of presentation (sustained tachyarrhythmia, severe hypertension with or without left ventricular hypertrophy (LVH), brady-arrhythmia, respiratory failure with severe hypoxaemia, anaemia, and hypotension/shock)¹ remain relevant to T2MI in this classification. Moreover, use of coronary angiography for diagnosis and management of specific entities (SCAD, coronary embolism, and vasomotor abnormalities) [3,4] remains determinant.

CAD has been reported as an important determinant in T2MI categorization and fixed stable coronary atherosclerosis, and support of myocardial oxygen balance mismatch, thus emerging as a key factor in T2MI pathophysiology [1]. In a recent meta-analysis, obstructive CAD was found in 34% of patients who underwent coronary angiography [5], and up to 61.2% in previous studies, depending on the threshold considered (50-70%) [6]. Uncertainty remains around the prognostic value of CAD among patients with T2MI [7–9], which could be a predictor for T2MI comparing to T1MI diagnosis [7], or an independent predictor for major adverse cardiac events (MACE) [8]. In context of T2MI, how the heterogeneous mechanisms for supply/demand

imbalance and non-coronary triggers leading to myocardial ischemia could be modulated by the presence and the severity of CAD [10] remains poorly understood.

From a large regional database of acute MI, we aimed to identifying the impact of the novel proposed classification of MI, based on both pathogenesis and CAD, on epidemiology and prognosis across the whole spectrum of type 1 and type 2 MI.

Patients and methods

Study population, selection criteria

This study was conducted using data from the obseRvatoire des Infarctus de Côte d'Or (RICO). RICO is a large ongoing survey that prospectively collects data from all consecutive patients aged 18 years-old, hospitalized for an acute MI in the 6 intensive care units (ICU) in an eastern region of France since 2001 [1]. For the present study, patients hospitalized for an acute MI between 2012 and 2017 were included. Acute MI was diagnosed according to the fourth UDMI criteria [1].

The adjudication of MI cases into T1MI and T2MI was retrospectively performed according to the new classification [3] by two trained cardiologists. Each case was reviewed and adjudicated by the two independent reviewers. Discrepancies were resolved by consensus, after an in-depth review of medical records. If disagreement persisted, the decision was made by a third independent cardiologist. MI were defined according to the current universal definition, i.e. rise of cardiac troponin above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischemia, new significant ST changes or new bundle branch block, or development of pathological Q waves [1, 12]. T1AMI was defined as acute coronary obstruction or reduction in coronary blood flow due to atherosclerotic plaque disruption (rupture or erosion) [1]. Other types of MI (Type 3 MI; Type 4a MI; Type 4b MI; Type 4c MI; Type 5 MI) were not included in the study. T2MI was defined as MI with evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary athero-thrombosis [1].

Underlying pathophysiological mechanisms of T2MI (except SCAD, coronary embolism and vasomotor abnormalities) were defined according to the 4th UDMI including sustained tachyarrhythmia, severe hypertension with or without left ventricular hypertrophy, severe brady-arrhythmia, respiratory failure with severe hypoxaemia, anaemia, and hypotension/shock [1]. These conditions were defined as follows:

- Sustained tachy-arrhythmia (i.e. atrial fibrillation (AF) or flutter): supraventricular tachy-arrhythmia \geq 20 min with a ventricular rate >150 beats/min [13],
- Severe hypertension: systolic blood pressure > 160 mmHg, with or without concomitant LVH identified by echocardiography [13],
- Severe brady-arrhythmia: brady-arrhythmia requiring medical treatment or pacing [13],

- Respiratory failure: clinical signs of acute respiratory distress lasting ≥ 20 minutes and arterial oxygen tension $< 8\text{kPa}$ [14],
- Severe anaemia: hemoglobin concentration $< 5.5\text{ mmol/L}$ for men and $< 5.0\text{ mmol/L}$ for women (measured on admission) and/or the need to use blood products [13],
- Hypotension/shock: systolic BP $< 90\text{ mmHg}$ and/or diastolic BP $< 60\text{ mmHg}$ associated with evidence of systemic hypo-perfusion (e.g. hyperlactatemia) and low cardiac output.

Systemic Inflammatory Response (SIRS) was diagnosed by at least two of the following criteria: body temperature over 38°C or under 36°C , heart rate > 90 beats/minute, respiratory rate > 20 breaths/minute or partial pressure of $\text{CO}_2 < 32\text{ mmHg}$, and leucocyte count > 12000 or $< 4000/\mu\text{liters}$ [15].

SCAD was defined as spontaneous dissection of the coronary artery wall with accumulation of blood within the false lumen, which can compress the true lumen to varying degrees [16]. Coronary spasm, refers to a sudden, intense vasoconstriction of an epicardial coronary artery that causes vessel occlusion or near occlusion on coronary angiography, even in the absence of stimulation [12]. Catheter-induced spasm limited to the first millimeters of the coronary artery was not considered. Coronary embolism, defined as a high thrombus burden despite a relatively normal underlying vessel or recurrent coronary thrombus (left heart endocarditis, intracardiac mural thrombus, documented venous thrombus, and a patent foramen ovale or atrial septum defect) [13].

SCAD, coronary embolism and vasomotor abnormalities (vasospasm or microvascular dysfunction) were categorized as T1BMI, T1CMI and T1DMI, respectively. T2MI was divided into 2 groups: T2AMI with obstructive CAD ($\geq 50\%$ coronary stenosis in at least 1 epicardial vessel), and T2BMI in the absence of obstructive CAD. “T2MI without angiography” had at least one underlying mechanism of T2MI, but didn’t undergo coronary angiography.

Data collected

For each patient, demographic data (age, gender), CV risk factors, chronic treatments and history, were collected as were on-admission clinical data, and ECG as described previously [13]. Obesity was defined as body mass index $\geq 30\text{ Kg/m}^2$. Length of ICU stay and Global Registry of Acute Coronary Event (GRACE) score for mortality risk estimation were also reported [17]. Blood samples were taken on admission to measure haemoglobin, C-reactive protein (CRP), B-type natriuretic peptide (NTproBNP) and creatinine levels. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI). Cardiac troponin I (Ic) peak was assessed by sampling every 8 hours during the first 2 days after admission. Left ventricle ejection fraction (LVEF) was measured by transthoracic echocardiography within 48 hours after admission.

LVEF value was cut at 40% for more clinical relevance. Coronary angiography and percutaneous coronary intervention (PCI) were performed according to routine clinical practice. Significant lesions were defined by coronary stenosis $\geq 50\%$, and the coronary lesion severity was assessed by SYNTAX score [18].

In-hospital events after ICU admission were recorded including severe heart failure (maximum Killip >2), stroke, recurrent infarction, AF/Flutter, severe bleeding (defined as BARC type 3b) and all-cause and CV death. Acute (< 48 h) and at discharge treatments were also collected. One-year death was recorded by mailing or phone interview to the patients, family or general practitioner. Mortality was considered as CV related if due to myocardial infarction, stroke, ventricular arrhythmias, or in cases of sudden unexpected death.

Ethics

The present study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Dijon University Hospital. Each patient gave written consent before participation.

Statistical analysis

The categorical variables were expressed as numbers and percentages and compared using the chi-squared test or Fisher exact test. The quantitative variables were expressed as medians with interquartile ranges and compared using the ANOVA test or the Mann-Whitney test. The normality of the variables was determined using Kolmogorov-Smirnov test. Significance was set at $p < 0.05$.

Kaplan-Meier one-year survival curves (all-cause and cardiovascular mortality) were analyzed, and compared by log-rank test.

A Cox multivariate regression analysis was performed to assess predictors of all-cause and CV mortality. Multivariate models were built by including predictive variables in univariate analysis, with an inclusion threshold of $p < 0.01$, and prespecified variables: age, gender and type of MI. The final model was chosen by the best quality index, i.e. lowest likelihood estimate and highest area under curve. Statistical analyses were performed using SPSS software version 12.0.1 (IBM Inc., NY). We defined statistical significance using a two-sided P-value < 0.05 .

Results

Epidemiological data

Among the 4573 patients included, 3710 (81.1%) were initially diagnosed with T1MI and 863 (18.9%) with T2MI. Ninety-six T2MI patients (11.1 % of all T2MI) were moved into the T1MI category, based on the new classification (i.e. SCAD, coronary embolism, and coronary vasomotor abnormalities (including vasospasm and microvascular dysfunction)). Out of the remaining 767 patients with T2MI, most (567) underwent coronary angiography, of whom 389

(68.6%) had fixed obstructive CAD (T2AMI) and 178 patients (31.4%) had no obstructive CAD on coronary angiography, and classified as T2BMI. Coronary angiography was not performed in 200 patients with type 2 MI (T2MI without angiography). The flow chart of the distribution of MI subtypes is shown in Figure 1.

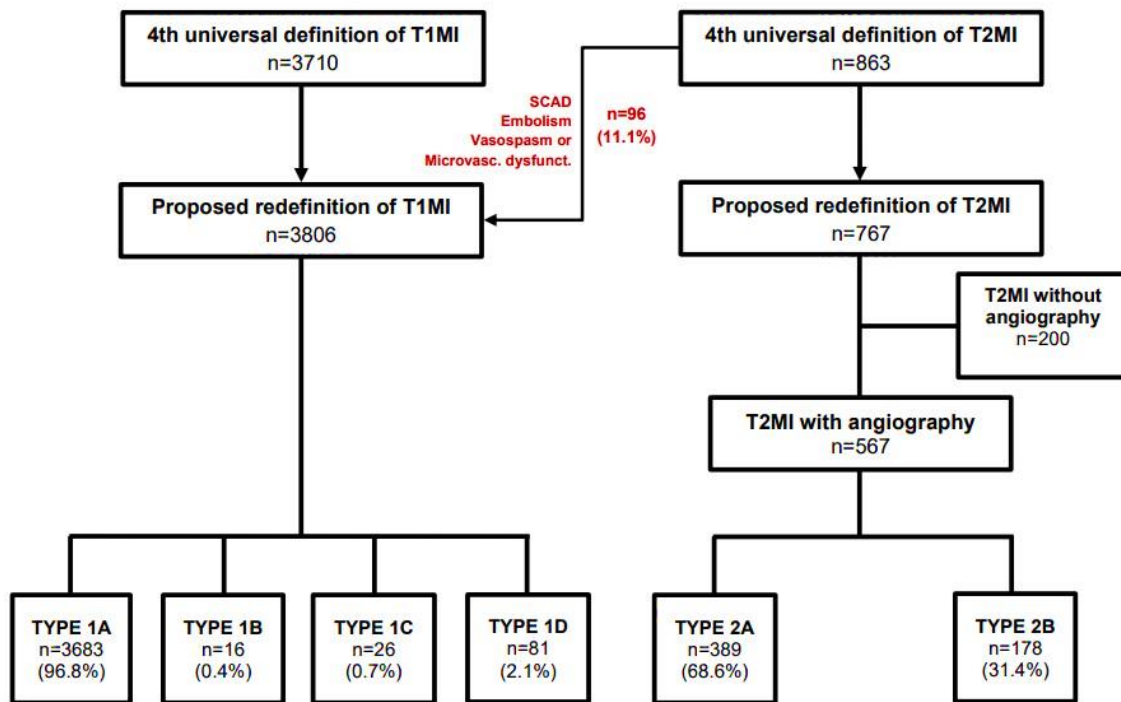


Figure 1: Figure 1. Flow chart of the study according to the proposed modification of the 4th Universal Definition of Myocardial Infarction.

T1MI : Type 1 myocardial infarction (myocardial infarction with acute coronary obstruction)

T2MI : Type 2 myocardial infarction (myocardial infarction due to oxygen supply/demand without coronary obstruction)

Type 1A : plaque rupture/erosion with thrombus

Type 1B : spontaneous coronary artery dissection

Type 1C : coronary embolism

Type 1D : vasospasm or microvascular dysfunction

Type 2A : with fixed obstructive coronary artery disease

Type 2B : without fixed obstructive coronary artery disease

Both Kappa statistics (K 0.702, 95%CI 0.675-0.730) and Gwet's AC₁ (AC₁ 0.878; 95% CI 0.866–0.891) gave a substantial level of agreement in adjudication of MI cases (**Supplemental Table 1**).

Underlying mechanisms according to T2MI categories (with or without CAD) are shown in **Figure 2**. Anemia and SIRS were the main causal factors characterizing T2AMI subgroup ($p < 0.001$). In contrast, tachy-arrhythmia was much more common in patients without obstructive CAD (T2BMI) ($p < 0.001$). The other mechanisms were similar for the 2 groups.

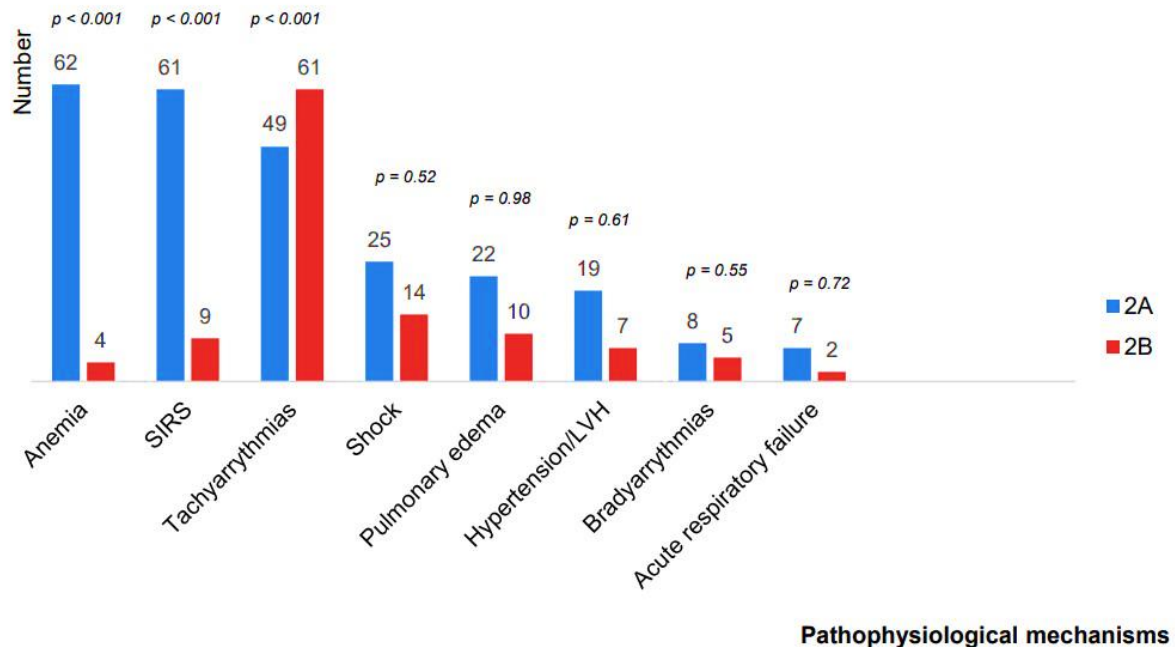


Figure 2: Figure 2. Pathophysiological mechanisms of type 2A and type 2B myocardial infarction.

Characteristics, risk factors and management

Table 1 summarizes the characteristics of the study population, according to T1AMI, T2AMI and T2BMI patients.

Table 1: Patients characteristics (n(%) or median [IQR]).

	Type 1A n = 3683	Type 2A n = 389	Type 2B n = 178	<i>p</i>
Risk factors and comorbidities				
Age, years	67 [56-79]*	78 [69-84] ^S	73 [61-82] [#]	< 0.001
Female	961 (26.1)*	143 (36.8) ^S	98 (55.1) [#]	< 0.001
BMI, kg/m ²	27 [24-30]	26 [23-29]	26 [23-30]	0.226
Obesity (BMI ≥ 30 Kg/m ²)	950 (26.0)	96 (24.8)	48 (27.3)	0.806
Hypertension	2138 (58.1)*	313 (80.5) ^S	119 (66.9) [#]	< 0.001
Hypercholesterolemia	1735 (47.1)*	228 (58.6) ^S	80 (44.9)	< 0.001
Family history of CAD	1089 (29.6)	98 (25.2)	41 (23.0)	0.023
Current Smoking	1156 (31.4)*	55 (14.1)	29 (16.3) [#]	< 0.001
Diabetes	867 (23.5)*	162 (41.6) ^S	43 (24.2)	< 0.001
Chronic renal failure	170 (4.6)*	61 (15.7) ^S	5 (2.8)	< 0.001
Cardiovascular history				
CAD	826 (22.4)*	178 (45.8) ^S	29 (16.3)	< 0.001
Stroke	250 (6.8)*	63 (16.2)	19 (10.7) [#]	< 0.001
PAD	322 (7)*	105 (27) ^S	11 (6.2)	< 0.001
Heart failure	133 (3.6)*	40 (10.3)	13 (7.3) [#]	< 0.001
Atrial fibrillation	289 (7.8)*	69 (17.7)	41 (23.0) [#]	< 0.001
Chronic medication				
Beta-blockers	1066 (28.9)*	204 (52.4) ^S	64 (36.0) [#]	< 0.001
Aspirin	927 (25.2)*	179 (46.0) ^S	40 (22.5)	< 0.001
P2Y12 inhibitors	385 (10.5)*	96 (24.7) ^S	22 (12.4)	< 0.001
DOA	53 (1.4)	10 (2.6)	4 (2.2)	0.179
VKA	229 (6.2)*	75 (19.3)	35 (19.7) [#]	< 0.001
Statins	1105 (30.0)*	190 (48.8)	52 (29.2) [#]	< 0.001
Clinical & hemodynamic data at admission				
HR, beats/min	77 [66-90]*	84 [71-102] ^S	93 [77-115] [#]	< 0.001
SBP, mmHg	140 [120-160]	138 [118-160]	128.5 [112-156] [#]	0.022
DBP, mmHg	80 [70-93]*	76 [63-86]	75 [65-89] [#]	< 0.001
Anterior wall location	1343 (36.5)	144 (37.0)	55 (30.9)	0.305
GRACE risk score	143 [120-170]*	174 [149-197] ^S	160.5 [134-189] [#]	< 0.001
KILLIP admission > 1	807 (21.9)*	201 (51.7) ^S	67 (37.6) [#]	< 0.001
ECG at admission				
STEMI	1921 (52.2)*	106 (27.2) ^S	32 (18.0) [#]	< 0.001
AF/Flutter	262(7.1)*	69(17.7)	41(23.0) [#]	< 0.001
Biological data				
Hemoglobin, g/100mL	14.4 [13.0-15.4]*	12.4 [10.3-13.9] ^S	13.6 [12.2-15.1] [#]	< 0.001
CRP, mg/L	4.6 [2.9-12.0]*	16.0 [4.7-64.4] ^S	6.2 [2.9-27.4] [#]	< 0.001

Creatinine, $\mu\text{mol/L}$	83 [70-102]*	97 [73-126] ^S	85 [67-113]	< 0.001
eGFR, mL/min/1.73m^2	78.9 [58.8-94.1]*	58.7 [39.9-82.2] ^S	69.9 [50.4-83.8] [#]	< 0.001
Troponin Ic peak, $\mu\text{g/L}$	17.0 [3.4-68.0]*	5.3 [1.3-15.0] ^S	1.4 [0.5-5.2] [#]	< 0.001
NT-proBNP, pg/mL	578 [150-2334]*	3606 [1264-9615] ^S	1646 [511-5515] [#]	< 0.001
Echocardiography	n=3534	n=380	n=170	
LVEF, %	55 [45-60]*	48.5 [40-60] ^S	55 [40-62] [#]	< 0.001
LVEF \leq 40%	806 (22.8)*	132 (34.7)	49 (28.8)	< 0.001
ICU stay, days	4 [3-5]*	4 [3-6] ^S	3 [2-5] [#]	< 0.001
Normal coronary arteries	10 (0.3)	0 (0) ^S	102 (57.3) [#]	< 0.001
Number of significant lesions				
0	52 (1.4)*	0 (0) ^S	178 (100) [#]	< 0.001
1-vessel disease	1401 (38.0)*	101 (26.0) ^S	0 (0) [#]	< 0.001
2-vessel disease	1076 (29.2)*	102 (26.2) ^S	0 (0) [#]	< 0.001
3-vessel disease or LM	1154 (31.3)*	186 (47.8) ^S	0 (0) [#]	< 0.001
SYNTAX Score	11 [6-18]*	14 [7-22] ^S	0 [0-0] [#]	< 0.001

IQR: Interquartile range; BMI: body mass index; CAD: coronary artery disease; PAD: peripheral arterial disease; DOA: direct oral anticoagulant; VKA: vitamin K antagonist; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; STEMI: ST segment elevation myocardial infarction; AF: atrial fibrillation; CRP: C-reactive protein; eGFR: estimated Glomerular Filtration Rate; NT-proBNP: N-Terminal pro Brain Natriuretic Peptide; LVEF: left ventricular ejection fraction; ICU: intensive care unit. LM: left main.

$p < 0.05$ for *Type 1A versus 2A; [#]Type 1A versus 2B; ^SType 2A versus 2B.

When compared with patients without obstructive CAD (T2BMI), patients with obstructive CAD (T2AMI) were older, more frequently men, with co-morbidities including hypertension, hypercholesterolemia, diabetes, kidney failure and as expected, prior vascular disease. MI severity indexes, as assessed by rate for STEMI, LVEF and troponin Ic peak, were the highest among T1MI. Remarkably, CRP levels were higher in T2AMI patients ($p < 0.001$).

Coronary angiographic data are shown in **Table 1**. Compared to T1AMI group, T2AMI patients had much severe CAD burden, characterized by a higher SYNTAX score and more frequent 3-vessel or left main disease ($p < 0.001$). When compared with the 2 other groups, T2BMI patients were less aggressively treated by CV medications including statin, antiplatelets, and angiotensin-converting enzyme inhibitors/angiotensin II receptors blockers (ACEi/ARB) at both the acute and discharge phases than T1AMI and T2AMI (**Table 2**).

Table 2: Management

	Type 1A n = 3683	Type 2A n = 389	Type 2B n = 178	<i>p</i>
<i>Acute treatment</i>				
PCI	2956 (80.3)*	190 (48.8) [§]	0 (0) [#]	< 0.001
PCI or CABG	3127 (84.9)*	210 (54.0) [§]	0 (0) [#]	< 0.001
Aspirin	3587 (97.4)*	362 (93.1)	159 (89.3) [#]	< 0.001
P2Y12 inhibitors	3518 (95.5)*	312 (80.2)	131 (73.6) [#]	< 0.001
Beta blockers	2605 (70.7)	260 (66.8) [§]	101 (56.7) [#]	< 0.001
Statins	3276 (88.9)*	327 (84.1) [§]	120 (67.4) [#]	< 0.001
ACEI/ARB blockers	2132 (57.9)*	183 (47.0) [§]	68 (38.2) [#]	< 0.001
Diuretics	981 (26.6)*	223 (57.3) [§]	82 (46.1) [#]	< 0.001
DOA	32 (0.9)*	11 (2.8)	6 (3.4) [#]	< 0.001
VKA	187 (5.1)*	44 (11.3)	28 (15.7) [#]	< 0.001
<i>Treatment at discharge</i>				
Aspirin	3394 (92.2)*	332 (85.3) [§]	82 (46.1) [#]	< 0.001
P2Y12 inhibitors	3022 (82.1)*	216 (55.5) [§]	30 (16.9) [#]	< 0.001
Beta blockers	2992 (81.2)*	297 (76.3) [§]	105 (59.0) [#]	< 0.001
Statins	3248 (88.2)*	318 (81.7) [§]	100 (56.2) [#]	< 0.001
ACEI/ARB blockers	2853 (77.5)*	256 (65.8) [§]	95 (53.4) [#]	< 0.001
Diuretics	875 (23.8)*	184 (47.3) [§]	68 (38.2) [#]	< 0.001
DOA	36 (1.0)*	15 (3.9) [§]	13 (7.3) [#]	< 0.001
VKA	336 (9.1)*	91 (23.4)	44 (24.7) [#]	< 0.001

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; DOA: direct oral anticoagulant; VKA: vitamin K antagonist.

$p < 0.05$ for *Type 1A versus 2A; [#]Type 1A versus 2B; [§]Type 2A versus 2B.

The characteristics of T1BMI, T1CMI and T1DMI and T2MI without angiography are available in Supplemental material (**Supplemental Tables 2-5**).

Anticoagulants were likely to be more prescribed in this T1CMI subgroup. Moreover, T1CMI patients were older, more frequently women, with history of heart failure and related chronic medications, more heart failure at admission and during in-hospital stay, and a lower LVEF (**Supplemental Tables 2-4**).

Outcomes

When compared with T1AMI and T2BMI, T2AMI patients had worse more in-hospital events after ICU admission, including severe heart failure ($p < 0.001$), atrial fibrillation or flutter ($p < 0.001$) and severe bleeding ($p < 0.001$) (**Table 3**). Moreover, T2AMI showed a trend toward a highest all-cause and cardiovascular mortality (**Table 3**).

Table 3: In hospital events after ICU admission (n(%)).

	Type 1A n = 3683	Type 2A n = 389	Type 2B n = 178	<i>p</i>
Severe heart failure	415 (11.3)*	128 (32.9) [§]	31 (17.4) [#]	< 0.001
Ischemia				
Recurrent Infarction	126 (3.4)	13 (3.3) [§]	1 (0.6) [#]	0.113
Stroke	36 (1.0)	8 (2.1)	3 (1.7)	0.096
Rhythm and conduction				
AF/Flutter	263 (7.1)*	66 (17.0)	22 (12.4) [#]	< 0.001
Cardiac arrest	8 (0.2)	1 (0.3)	0 (0.0)	0.725
Bleeding complications				
Severe bleeding	180 (4.9)*	42 (10.8) [§]	8 (4.5)	< 0.001
Death				
All cause	194 (5.3)*	30 (7.7)	11 (6.2)	0.124
Cardiovascular cause	181 (4.9)	25 (6.4)	10 (5.6)	0.411

AF: Atrial fibrillation. ICU: Intensive care unit.

Severe heart failure: maximum KILLIP class > 2. Severe bleeding: BARC definition type 3b.

p < 0.05 for *Type 1A versus 2A; [#]Type 1A versus 2B; [§]Type 2A versus 2B.

After one-year follow-up, crude all-cause (20.3%) and CV mortalities (13.4%) were higher in T2AMI than T1AMI and T2BAMI (*p* < 0.001). Kaplan Meier survival curve analysis (**Figure 3**) also showed the worse survival in T2AMI than in other types (*p*<0.001).

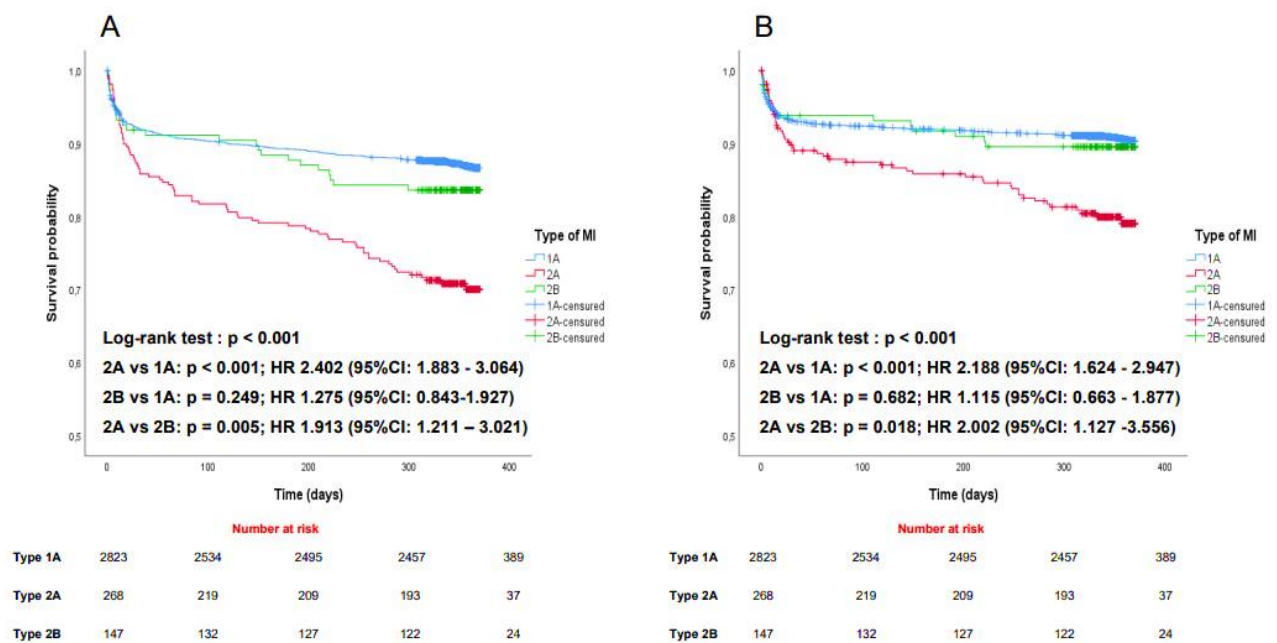


Figure 3: Kaplan Meier one-year all-cause mortality (A) and cardiovascular mortality (B) survival curves according to types 1A, 2A and 2B myocardial infarction

Univariate Cox regression analyses for the estimates associated with 1-Y mortality are available in Supplemental material (**Supplemental Tables 6-7**). By multivariate regression analysis, type of MI was an independent estimate of mortality (**Figure 4**) and T2AMI remains at higher risk for all-cause mortality, even after adjustment for confounding factors, including age (HR 1.362; 95%CI 1.029-1.802). In contrast, T1AMI was at higher risk for CV mortality, when compared with both types of T2MI, and even after adjustment for traditional risk factors.

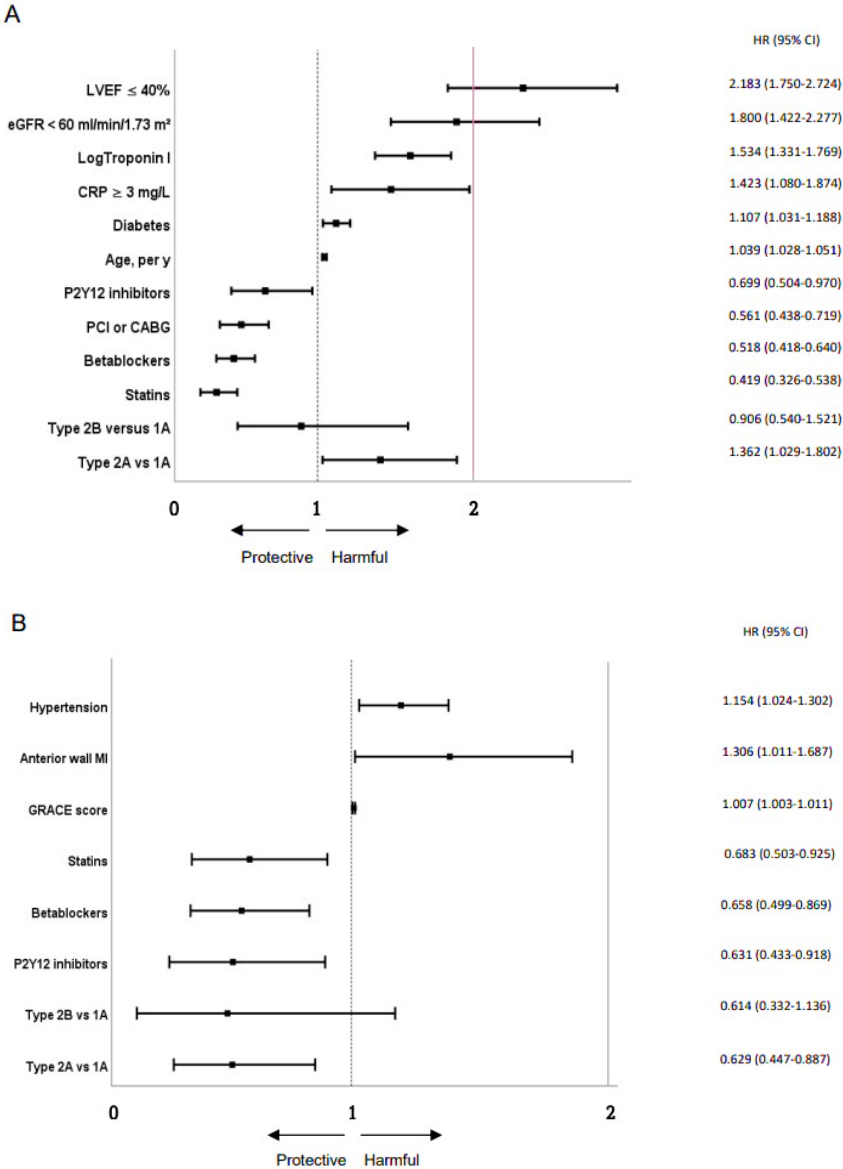


Figure 4: Cox multivariate analysis of all-cause mortality (A) and cardiovascular mortality (B). Forest plots.

Discussion

Observational studies have shown that T2MI is common in clinical practice and associated with substantial risk for adverse outcomes. However, T2MI, as a condition of supply/demand oxygen imbalance, remains largely underrecognized, partly caused by varying definitions, difficulties in cases adjudication, heterogenous phenotypes and lack of specific treatment strategies. New approaches are thus needed to improve our knowledge on T2MI characteristics and management. Our findings from a large regional survey, with systematic MI types adjudication over a 6-year period, provides contributive data on the impact of a new proposal on MI classification, and further insights on the role of CAD in such enigmatic pathology. These works further support the consideration of CAD as a frequent and major prognostic determinant of T2MI. To date, the prognostic impact of CAD among T2MI patients have not been yet extensively described. Although de Lemos was the first to propose a new classification of MI, CAD as a key issue in type 2 MI was previously raised in some studies. Few studies specifically addressed the short and long-term impact of documented CAD among patients with T2MI. In-hospital all-cause mortality risk increased by twofold in T2MI patients, considering T1MI and T2MI with significant CAD (15% vs. 7%, $p < 0.001$) [7]. After long-term follow-up, T2MI patients with CAD showed higher crude long-term all-cause mortality as compared with T1MI patients with obstructive CAD (HR 1.72; 95%CI 1.45-2.03) [32]. Moreover, in a monocenter study including 2122 patients [35], CAD was an independent predictor of MACE at 5 years in patients with T2MI or myocardial injury (HR 1.71; 95%CI 1.31-2.24), emphasizing the prognostic role of CAD in T2MI. Moreover, the importance of ischemic heart disease, as a strong component of T2MI prognosis was also recently emphasized by the development of new risk scores, such as the T2-risk score including coronary artery disease as a main variable [54]. Higher T2-risk scores were associated with occurrence of subsequent MI or all-cause death at 1 year [54]. In a previous study, CAD was already identified as a key variable in the development of a score in order to distinguish T2MI from T1MI patients [55].

To the best of our knowledge, this study is one of the first to comprehensively address MI types including T1MI (1A, 1B, 1C and 1D) and T2MI (2A, 2B, 2C and 2D) subgroups, based on the proposed definition of de Lemos 44. Main changes concerns T2MI, a tiny tad more homogenous (with/without CAD), while T1MI reclassification is only slightly different. Prevalence of T1MI subgroups are quite consistent with the recent findings [56], in which T1BMI and T1CMI were rare ($< 1\%$), and only a minor proportion of patients presented vasospasm or microvascular dysfunction (2.1%). Among type 1 MI, the main group is represented by the classical T1AMI, corresponding to T1MI, defined by the 4th UDMI. T2MI are characterized by marked predominance of T2AMI, and low rate of T2BMI. It may be selection bias induced by the so called "T2MI patients without coronary angiography" (n=200),

avoiding the adjudication as T2AMI or T2BMI. Based on the 4th UDMI guidelines, coronary angiography is not required to establish the diagnosis of T2MI. Visualization of plaque rupture with thrombus could help to differentiate between T1MI and T2MI. Nevertheless, plaque disruption or intracoronary thrombus are not limited to T1MI, and may be identified by intravascular ultrasound imaging even in stable CAD or asymptomatic patients [27]. Ongoing randomized trial should provide more comprehensive data on the appropriateness of coronary investigation in patients with T2MI [57].

Although CAD is common among T2MI patients undergoing coronary angiography, there is a wide range of CAD rates across studies [28]. A contemporary work found up to 68% prevalence of CAD in T2MI patients, which was obstructive in 30% of cases [33]. The nationwide SWEDEHEART registry also showed a high rate of CAD among T2MI patients (57.6%), similar to our study [58]. In the single center CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) study [31], prospectively including T2MI patients undergoing coronary angiography with or without intervention, more than 60% of patients had two-vessel CAD ($\geq 50\%$ coronary stenosis).

In addition to CAD, other chronic or acute conditions are involved in the pathogenesis of T2MI. We found that anemia and SIRS were major underlying mechanisms in T2AMI. Recent data from the High-STEACS registry suggested tachyarrhythmia (55%), hypoxemia (20%) and anemia (9%) as the main triggering factors in T2MI [59]. Anemia, as an aggravating factor for myocardial ischemia, is recognized as one of the main chronic condition associated with T2MI, with a wide range of rate ranging from 7.8 to 39% [60]. Moreover, in a recent study, anemia was a predictor of 30-day readmission in patients hospitalized for T2MI [61]. Compared to T1MI, T2MI owing to anemia were at greatest risk of death (aOR, 1.83; 95% CI, 1.14-2.88) [59]. Interestingly, anemic patients were often under antiplatelet agents (aspirin and clopidogrel) and anticoagulants, which could aggravate anemia in frailty patients.

The role of inflammation as a key determinant in the pathogenesis of atherosclerotic disease has been extensively described. Elevated CRP levels in the T2AMI group are consistent with older age [62] and with chronic inflammation associated with obstructive coronary lesions [63]. However, it may also be partly linked to SIRS-related acute inflammation. Elevated CRP (defined as > 3 mg/L) has been associated with T2MI and history of CAD [36] further supporting the hypothesis that inflammation plays a role in the pathophysiology of T2MI. T2MI are usually associated with much lower troponin values than T1MI [64] and CRP/troponin ratio has been shown to provide the best predictive value for T2MI [36]. Indeed, sepsis is mainly related to myocardial injury according to the fourth UDMI. In our series, patients with SIRS adjudicated as T2MI had evidence of ischemia, attested by clinical symptoms and dynamic ECG changes apart from troponin elevation. Unfortunately, multimodality imaging (i.e. cardiac magnetic

resonance...) was not always performed to ascertain the diagnosis of MI. Sepsis is not exclusive from MI, as some cases of infectious-related MI have been reported, and particularly well described in the era of COVID-19. In a previous study [45], we aimed to evaluate the respective part of acute infection in the pathogenesis of T2MI and non-ischemic myocardial injury (NIMI). Among 4436 patients admitted in the emergency department with troponin elevation, 1453 (33%) had NIMI and 947 (21%) had T2MI. The proportion of patients presenting with a diagnosis of acute infection at admission was very high and similar in the two groups (36%). Thus, sepsis appears to be involved in both NIMI and T2MI pathogenesis.

We found that tachy-arrhythmias (particularly AF) was a major acute trigger for T2MI. A recent literature review also reported that tachy-arrhythmias is a common trigger for T2MI, with a rate ranging from 13 to 47% [60]. Moreover, AF is a predictor for in-hospital mortality and 30-day rehospitalisation in patients with T2MI [61].

We used for diagnosis purpose a conventional cTnI assay, which has a lower sensitivity, and approximatively 10% coefficient of variation at the 99th percentile. cTnI assay use may lead to lower identification of significant sample changes to identify MI [65]. However, in a recent meta analysis, only 4 of the 40 studies reported the use of high sensitivity cTn assays; conventional cTnI was the most widely used [30], thus reflecting real-life practice in numerous heart centres. Patients with T2AMI had higher one-year all-cause mortality compared to T1MI and T2BMI, after adjustment for confounding including age and co-morbidities. In T2MI patients, the prognostic value of obstructive CAD had been addressed for both short and long term [32,35,36]. Data in the literature indicate that patients with T2MI have higher all-cause mortality compared to T1MI, mostly driven by non-cardiovascular causes [28,66], even if cardiovascular death was common among T2MI patients in some long-term studies, accounting for 24-43% of deaths [31,35,67], or in younger subjects (≤ 50 yo) [68]. Patients with T2MI are characterized by older age and comorbidities [45,69], thus increasing the risk of all-cause death in this specific population. Noteworthy, deaths in T1MI patients are more likely from cardiovascular causes [67,70]. In a study by Lambrecht et al, including 3762 patients with mean follow-up of 3.2 years, 61.3 % of T1MI patients died from cardiovascular causes versus 42.6 % in T2MI patients ($p=0.015$) and 41.2 % in those with myocardial injury ($p<0.0001$) [67]. Our study, after one-year follow-up, demonstrated that T2MI were less likely to die from cardiovascular causes than T1MI in multivariate analysis, after adjustment. In another studies, no difference was observed between the two groups concerning cardiovascular death [66,71].

Study strengths and limitations

Our study has some limitations. The diagnosis was prospectively set by internal processes, without external validation. However, the adjudication procedures including inter-observer agreement consensus is assumed to avoid major misclassifications. As reported by McCarthy

et al [72], despite strict adjudication, only 56.7% of patients identified as T2MI had really T2MI, and 41.9% had myocardial injury. These data showed that myocardial injury is often miscoded. As our study used cTnI, the prognostic implication of our findings cannot be extrapolated to cohort that would use high sensitivity (hs) TnI. More MI cases (especially type 2 MI, for which TnI levels are lower) would have been identified with the implementation of hs TnI. In addition, some clinical variables, particularly sex, may affect cTn concentrations beyond MI. However, current data on the use of sex-specific cTn values in the diagnosis of MI have been controversial [73] and currently, the use of uniform unique sex-independent cut-off concentration is considered as the standard of care for the early diagnosis of MI [74].

Among the patients with T2MI, 200 (26.1 %) patients who did not perform coronary angiography could not be assigned in T2AMI and T2BMI. The proposed revision of de Lemos in fact applies to patients who have undergone coronary angiography. Moreover, despite current guidelines, angiography was sometimes performed based on clinical judgment. This study was limited to ICU patients, although post-infectious MI frequently occurs in frail comorbid individuals hospitalized in other non-ICU departments [43]. Our work, focusing on ICU patients may have induced selection bias by excluding MI patients admitted in other units. Recent studies have shown that a considerable proportion of type 2 MI patients is managed in other wards outside ICU [42,43]. As we considered only MI patients in ICU, generalization of the results to all MI should be considered with caution. However, despite these short-comings, the rate of CAD found in our series was consistent with previous studies.

In T1DMI (MI related to vasospasm or microvascular dysfunction), provocation test (i.e. with ergonovine) to identify spastic mechanism was not performed, nor was the index of microcirculatory resistance to identify microvascular dysfunction [75]. Even though adjudication of patients in T1MI and T2MI sub-groups was made systematically by experienced cardiologists, classification errors may have been made, as some patients with T2MI (11.1%) were reclassified a posteriori.

In addition, T2MI definition was clinically based, according to guidelines⁸. In the absence of coronary imaging, atherothrombosis mechanism leading to MI could not be firmly excluded in some cases, where T2MI diagnosis was only speculative. However, coronary angiography and intracoronary imaging (intravascular ultrasound) analysis showed that plaque rupture is not specific for T1MI [27] and biomarkers are relevant for discrimination between T1MI and T2MI [36,64,76]. Moreover, cut-offs used to identify triggers of acute supply-demand mismatch in T2MI are not well defined to date, and therefore can not be generalized, given the high variability of individuals ischemic thresholds. Ischaemic thresholds in T2MI may vary substantially in individual patients depending on the magnitude of the stressor, the presence of non-cardiac comorbidities, and the extent of underlying CAD and cardiac structural

abnormalities [8]. Some studies have shown variable prevalences of type 2 MI, depending on criteria used for diagnosis. Unfortunately, for this study, we used fixed cut-offs to identify acute triggers involved in T2MI. Thus, we agree that some cases of T2MI may have been miscoded as T1MI, as patients with most severe CAD had probable lower tolerance to ischemia. However, in the absence of validated quantification measures for individual sensitivity to myocardial ischemia in routine MI management, we used the current criteria for adjudication. The same applies for T1MI, identified mainly on the basis of coronary angiography. Without intracoronary imaging, it's sometimes difficult to confirm the atherothrombosis phenomenon. The distinction between type 2 MI and myocardial injury diagnosis is a key issue, because the latter is commonly associated with acute heart failure and acute infection [15,28]. However, only patients with MI diagnosed on the basis of clinical, imaging, or ECG signs, as defined by the fourth UDMI, were included in this study. Acute heart failure and SIRS are not specific to T2MI; however, some cases of T2MI related to these conditions have been reported [77,78]. We separated knowingly from the main analyses T1BMI, T1CMI and T1DMI patients because of small populations often reducing the statistical power of analyses. We plan to make further analyses with larger samples.

Although the number of patients lost to follow-up was weak ($n=19$ (0.4%)), these patients may affect the results. However, they had characteristics similar to patients with follow-up, in particular for female rate ($p=0.186$), although they were slightly younger (61 vs 69 y, $p=0.018$). However, given this weak number of subjects lost to follow-up, we expect that they do not significantly impact the conclusions drawn by our findings.

Nevertheless, this study is one of the first to assess the new proposed classification of T1MI and T2MI, across the whole spectrum of MI, with complete in-hospital and coronary angiographic data and outcomes.

Conclusion

The objective of the proposed revision of MI classification was a better alignment of MI diagnosis with clinical presentation and pathophysiology, though reclassification of the 3 non-atherothrombotic causes of abrupt coronary obstruction from T2MI to T1MI, and distinction of CAD among T2MI. Our study, from a large MI database with systematic adjudication of MI types and causes, showed that the new classification opens new perspectives to the pathophysiological approach, identification, and management of T1MI and T2MI patients. Our findings, addressing the whole spectrum of specific causes of T2MI, identified preferential underlying mechanisms associated with CAD, such as anemia and SIRS and may help to better understand this enigmatic type of MI. Moreover, long-term follow-up highlighted the heavy prognostic burden of CAD in T2MI, further justifying the dichotomization between T2AMI

and T2BMI: Most patients with T2MI had obstructive CAD, a condition which increased the risk of death by almost 40%, requiring specific management. Given the gap in knowledge in management strategies for T2MI, our findings may help to personalized medicine in this frequent and fuzzy disease with major prognostic consequences. By characterizing patient subgroups that are more homogeneous in pathophysiological and prognostic terms, the modification proposed by Lemos et al. could meet the urgent need for standardization in the management of type 2 MI.

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Declarations of interest

None

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3.2. *Epidémiologie de l'infarctus du myocarde de type 2 dans une population d'Afrique Sub-Saharienne*

Cette 2^{ème} partie avait pour objectifs d'appréhender les enjeux démographiques et épidémiologiques des IDM type 2, dans la population spécifique de Côte d'Ivoire.

A notre connaissance, les données épidémiologiques sur l'IDM de type 2 en Afrique Sub-Saharienne n'ont jusque-là jamais été étudiées. La maladie coronaire, traditionnellement considérée comme rare en Afrique Sub-Saharienne, connaît une émergence récente ⁴² dans un contexte d'urbanisation et de modification du style de vie. Cette « transition épidémiologique » vers les MCV (en particulier la maladie coronarienne) survient dans une population jeune, à démographie dynamique et où le poids des facteurs de risque CV ne cessent de progresser. Nos travaux, soumis dans la revue *Journal of the American Heart Association*, ont inclus des données des patients hospitalisés pour IDM à l'Institut de cardiologie d'Abidjan (Côte d'Ivoire) entre 2018 et 2022.

La population de Côte d'Ivoire, estimée à plus de 29 millions d'habitants en 2021, est majoritairement urbaine (52,5%), et caractérisée par la diversité de ses origines ethniques ⁵². Il existe une forte croissance démographique (76% ont moins de 35 ans), avec une espérance de vie d'environ 53 ans ⁵³. La Côte d'Ivoire représente la plus forte économie de l'Union économique et monétaire ouest-africaine et connaît l'un des taux de croissance économique les plus rapides de l'Afrique subsaharienne depuis près d'une décennie ⁵⁴. Sur le territoire Ivoirien, la couverture sanitaire comprend 5 Centre Hospitaliers Universitaires (CHU) dont 4 à Abidjan, la capitale économique du pays, et plusieurs Centres Hospitaliers Régionaux (CHR), Hôpitaux Généraux (HG) et Formations Sanitaires Urbaines (FSU). Cependant, l'accès aux centres spécialisés pour la prise en charge des affections CV, en particulier l'IDM, est limité, comme dans la plupart des pays d'Afrique subsaharienne. Seuls quelques établissements, comme l'Institut de Cardiologie d'Abidjan, qui est le centre Ivoirien de référence, situé au sein du CHU

de Treichville, sont équipés de salle de cathétérisme cardiaque et d'USIC pour la prise en charge 24H/24 et 7j/7 de l'IDM ^{55,56,43}. Il était particulièrement pertinent d'analyser la prévalence et les spécificités des IDM type 2 dans cette population à l'aide d'un homologue de l'observatoire RICO, le registre REACTIV, dans un contexte de rareté des données sur l'IDM.

Type 2 myocardial infarction in a Sub-Saharan Africa population: challenging the current concepts. Data from the REACTIV registry

Running title: **Type 2 myocardial infarction in Sub-Saharan Africa**

Hermann Yao^{1,2}, Camille Touré², Arnaud Ekou², Elvis Sepih², Yves Cottin³, Marianne Zeller¹, Alain Putot^{1,4}, Roland N'Guetta²

¹ PEC2, EA 7460, UFR Health Sciences, University of Bourgogne Franche Comté, Dijon, France

² Abidjan Heart Institute, Côte d'Ivoire

³ Cardiology department, University Hospital Center Dijon Bourgogne, Dijon, France

⁴ Internal Medicine Department, Mont Blanc Hospital, Sallanches, France

Corresponding author:

Hermann YAO, MD, MPH

Abidjan Heart Institute, Boulevard de Marseille, 01 BP V 206 Abidjan, Côte d'Ivoire.

hermannyao@gmail.com

Abstract

Background: From a large observational acute coronary syndrome registry in Côte d'Ivoire, we aimed to assess incidence, clinical presentation, management, and in-hospital outcomes for type 2 myocardial infarction (T2MI) compared with type 1 MI (T1MI).

Patients and methods: We conducted a cross-sectional monocentric study using data from the REgistre des InfArctus de Côte d'Ivoire (REACTIV) at the Abidjan Heart Institute. All patients hospitalized with MI between 2018 and 2022 who underwent coronary angiography were included. Acute MI cases were classified as T1MI or T2MI based on criteria defined in the fourth universal definition of MI. For each patient, sociodemographic data, cardiovascular (CV) risk factors and history, and clinical and paraclinical presentation were collected at admission. Patients were followed up for in-hospital outcomes, including major adverse CV events (MACE) and mortality.

Results: Among 541 consecutive patients hospitalized with MI, coronary angiography was performed in 454 patients. Finally, 441 met the definition of T1MI or T2MI. T2MI accounted for 14.1% of cases (62/441). When compared with T1MI, T2MI patients were slightly younger (54 versus 58 years, $p = 0.09$) and more often women. Typical CV risk factors (hypertension, diabetes, dyslipidemia, and smoking) were more frequent in T1MI. T2MI patients had more frequent history of heart failure and left ventricular dysfunction ($p = 0.025$) and were more likely to have atrial fibrillation (AF)/flutter ($p < 0.001$). Compared to T1MI, T2MI had less severe CAD, with less frequent multivessel disease ($p < 0.001$). P2Y12 inhibitors were more likely to be prescribed in T1MI ($p < 0.001$). By contrast, vitamin K antagonists (VKA) were used only in T2MI patients. The main triggering factors for T2MI were coronary embolism (24.2%), severe hypertension \pm left ventricular hypertrophy (22.6%) and tachyarrhythmia (16.1%). Anemia was rarely involved (6.4%).

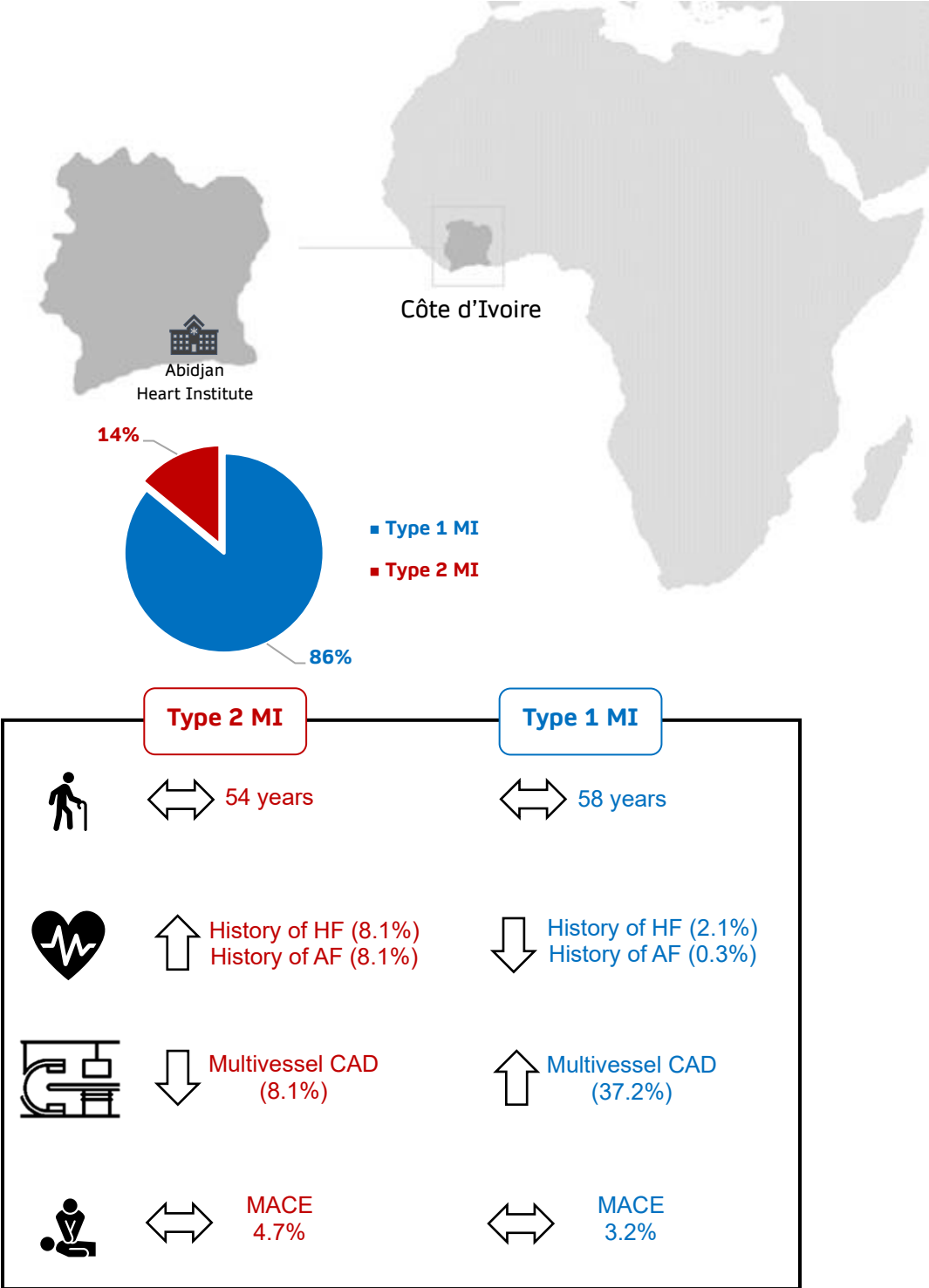
In-hospital event rates were low in both MI types. According to medical history and ECG findings, rates of AF/flutter and stroke were non-significantly higher in T2MI. Although the difference was non-significant, death rates in T1MI tended to be higher than in T2MI, as well as occurrence of MACE.

Conclusion: Our study, carried out over a 5-year period at the Abidjan Heart Institute, revealed significant disparities in clinical characteristics, angiographic features, etiology and in-hospital outcomes in T2MI in our population compared to Western populations. Compared with T1MI, T2MI was characterized by younger age, less frequent risk factors and more frequent AF/flutter. Coronary embolism was the main triggering factor in T2MI. T2MI patients had less severe CAD compared to T1MI. These results demonstrate the heterogeneity of T2MI and the

significant etiological and demographic variability depending on geographical area. It would be interesting to implement prospective multicenter studies in Sub-Saharan Africa in order to refine these results and assess the long-term prognosis of T2MI patients.

Key words: Type 1 myocardial infarction. Type 2 myocardial infarction. Coronary artery disease. Sub-Saharan Africa.

Graphical Abstract



INTRODUCTION

Myocardial infarction (MI) is the most common acute presentation of ischemic heart disease, which is the leading cause of death worldwide [1]. In Sub-Saharan Africa, acute MI has recently emerged as a major public health issue in association with the adoption of Western lifestyles. Accordingly, there has been a sharp rise in MI incidence, and high mortality rates have been reported across various studies [2]. Over the last two decades, in Côte d'Ivoire, hospital admissions for acute MI increased dramatically from 7.3% to 22.6% with an estimated in-hospital mortality rate of 10.4% [3].

MI has been defined by successive universal definitions, i.e. rise of cardiac troponin above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischemia, new significant ST changes or new bundle branch block, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of a coronary thrombus by angiography or by autopsy [4-6]. The universal classification of MI, which was introduced in 2007 including five clinical types, was revised in 2012 and again in 2018, resulting in the fourth universal definition of MI (UDMI) [4-6]. The most common type of MI, type 1 MI (T1MI), is defined as MI due to atherothrombotic mechanism (plaque disruption, rupture, or erosion), as a consequence of coronary atherosclerosis, associated with "classical" risk factors (including hypertension, smoking, dyslipidemia, diabetes, and obesity). Type 2 MI (T2MI), a heterogeneous group of acute coronary events, is defined as MI with evidence of a mismatch between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis. T2MI can have various triggers: vasomotor abnormalities (including vasospasm or microvascular dysfunction), coronary embolism, spontaneous coronary artery dissection (SCAD), sustained tachyarrhythmia, severe bradyarrhythmia, severe hypertension with or without left ventricular hypertrophy (LVH), respiratory failure with severe hypoxemia, anemia, and hypotension/shock [6]. Coronary angiography is important for the diagnosis of T2MI because it confirms that there is no visible coronary thrombosis [7].

The wide range of clinical presentations and multiple underlying mechanisms makes T2MI a diagnostic and therapeutic challenge, requiring tailored management. In Western populations, T2MI is common and is characterized by specific profiles, including older age and more comorbidities when compared to T1MI. Moreover, patients with T2MI have dramatically increased in-hospital [8,9] and long-term mortality [10].

In Sub-Saharan Africa countries, to the best of our knowledge, the epidemiology of MI types are unknown and no prospective study has specifically addressed T2MI. Côte d'Ivoire, classified as a lower-middle-income country by the World Bank, is the largest economy in the West African Economic and Monetary Union and is experiencing one of the fastest sustained

economic growth rates in Sub-Saharan Africa in nearly a decade [11]. It has a very young and active population and is currently undergoing major demographic growth. Similar to other Sub-Saharan African countries, the epidemiological transition has been marked by the recent emergence of cardiovascular diseases, particularly acute MI, in a context of urbanization and lifestyle changes [12]. In Côte d'Ivoire, as in most of Sub-Saharan Africa, there is limited access to heart centers where acute MI can be effectively managed. Only a few facilities, such as the Abidjan Heart Institute, are equipped with intensive care units (ICU) and cardiac catheterization laboratories [13,14].

From a prospective study in Côte d'Ivoire, we aimed to address incidence, clinical features, management, and in-hospital outcomes of T2MI compared with T1MI patients.

PATIENTS AND METHODS

Study design and patient criteria

We conducted a cross-sectional monocentric study using data from the REgistre des InfArctus de Côte d'Ivoire (REACTIV). REACTIV is an ongoing survey that prospectively collects data from all consecutive patients aged > 18 years old, hospitalized for acute MI in the intensive care unit (ICU) of the Abidjan Heart Institute [3]. It is the largest facility in Côte d'Ivoire and the national referral centre for the management of cardiovascular diseases, capable of providing cardiovascular care 24/24 and 7/7. The center includes an emergency department, an ICU, wards, a department for non-invasive exploration (including echocardiography laboratories and other cardiac diagnostic tests), a pediatric cardiology department, operating rooms for cardiovascular and thoracic surgery, an interventional cardiology laboratory and a cardiac rehabilitation department.

For the present study, all MI patients included between 2018 and 2022 who underwent coronary angiography were eligible. Acute MI was diagnosed and MI cases were adjudicated into T1MI and T2MI, based on criteria defined in the fourth UDMI [6], and variables were collected with standard definitions in agreement with the RICO study [15] in the context of a collaborative project (Dijon/Abidjan Cardiovascular Network). Each MI case was independently reviewed by two cardiologists. Disagreements (34 cases, i.e 7.7%) were resolved by consensus, and if necessary, by a third cardiologist. Briefly, T1MI was defined as acute coronary obstruction or reduction of coronary blood flow precipitated by atherosclerotic plaque rupture or erosion. T2MI was defined as MI with context of mismatch between oxygen supply and demand, triggered by an acute stressor. These conditions were defined as follows:

- Coronary spasm [5]: sudden, intense vasoconstriction of an epicardial coronary artery that causes vessel occlusion or near occlusion on coronary angiography, even in the

absence of stimulation; excluding catheter-induced spasm limited to the first millimeters of the coronary artery.

- Coronary embolism [16]: defined as a high thrombus burden despite relatively normal underlying vessels.
- SCAD [17]: defined as spontaneous dissection of the coronary artery wall with accumulation of blood within the false lumen, which can compress the true lumen to varying degrees.
- Sustained tachyarrhythmia, especially atrial fibrillation (AF) or flutter: supraventricular tachyarrhythmia ≥ 20 min with a ventricular rate >150 beats/min [16].
- Severe hypertension: systolic blood pressure > 160 mmHg, with or without concomitant LVH identified by echocardiography [16].
- Severe bradyarrhythmia: bradyarrhythmia requiring medical treatment or pacing [16].
- Acute respiratory failure [18]: clinical signs of acute respiratory distress lasting ≥ 20 minutes and arterial oxygen tension < 8 kPa.
- Severe anemia [16]: hemoglobin concentration < 5.5 mmol/L for men and < 5.0 mmol/L for women (measured on admission) and/or the need to use blood products.
- Hypotension or shock: systolic BP < 90 mmHg and/or diastolic BP < 60 mmHg associated with evidence of systemic hypoperfusion (e.g. hyperlactatemia) and low cardiac output.

MI types other than T1MI and T2MI were excluded (see Flow chart).

Data collection

For each patient, sociodemographic and anthropometric data (age, sex, body mass index (BMI)), clinical data (CV risk factors and history, presentation), and ECG were collected at admission. Variables were collected with standard definitions from the RICO study protocol [15].

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or treatment of previously diagnosed hypertension. Diabetes mellitus was defined as one of the following: fasting hyperglycemia ≥ 1.26 g/L, twice; hyperglycemia ≥ 2 g/L at any time of day; glycated hemoglobin $\geq 6.5\%$; or treatment of previously diagnosed diabetes mellitus. Hypercholesterolemia was defined as a total cholesterol concentration > 2.40 g/L and/or a low-density lipoprotein cholesterol concentration > 1.60 g/L, and a high-density lipoprotein cholesterol concentration < 0.40 g/L in men or < 0.50 g/L in women. Family history of CAD was defined as premature MI or sudden cardiac death (< 55 years in the patient's father or in a first-degree male relative; and < 65 years in the patient's mother or in a first-degree female relative). Obesity was defined as body mass index (BMI) ≥ 30 kg/m².

Left ventricular ejection fraction (LVEF) was measured at admission using transthoracic echography and biplane Simpson's method.

On admission, blood samples were taken to measure circulating levels of hemoglobin, C-reactive protein, NT-proBNP and creatinine. Cardiac troponin I (cTn I_c) peak was assessed by sampling every day during the first 3 days after admission. The estimated glomerular filtration rate (eGFR) was calculated using the MDRD (Modification of Diet in Renal Disease) formula. Percutaneous coronary interventions (PCI) were performed according to local clinical practice and based on current guidelines. Coronary angiography was considered normal when the angiographic images did not show any visible atheromatous plaque or spastic phenomena. Significant coronary artery disease (CAD) was defined as the narrowing of at least one coronary vessel $\geq 50\%$, and CAD severity was assessed by the number of epicardial vessels involved (1-vessel, 2-vessel or 3-vessel/left main CAD). Treatment data (revascularization procedures, drugs prescribed during hospitalization) were collected. In-hospital outcomes were recorded, including heart failure (maximum Killip ≥ 2) [19], stroke, sustained ventricular arrhythmia, high-degree atrioventricular block, AF/flutter, severe bleeding (defined as BARC type 3b) [20], all-cause/CV death, and major adverse cardiac events (MACE) defined as CV death, re-infarction or stroke [21].

Ethics

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Abidjan Heart Institute. Each patient provided consent prior to participation.

Statistical analyses

Qualitative variables were expressed as numbers and percentages and compared using the Chi² test or Fisher's exact test. Quantitative variables were expressed as medians and interquartile ranges and compared using the Student's t test or the non-parametric Mann-Whitney test. Agreement between the two independent reviewers was assessed using Cohen's Kappa statistics [22].

Statistical analyses were performed using SPSS 26.0.0.0 (IBM, Armonk, NY), with statistical significance defined as $p < 0.05$.

RESULTS

Characteristics, risk factors and management

During the study period, 561 MI patients were admitted to the Abidjan Heart Institute. Twenty patients (18 T1MI and 2 T2MI) were excluded from the analysis for missing data. Among the remaining 541 patients, 87 did not undergo coronary angiography. Finally, 441 patients met the definition of T1MI or T2MI in the study population. T2MI accounted for 14.1% of cases (62/441). The flow chart is shown in Figure 1.

Kappa statistics (K 0.791, 95%CI 0.707-0.875) gave a substantial level of agreement in adjudication of MI cases (Supplemental Table 1).

When compared with patients with T1MI, T2MI patients were slightly younger (54 versus 58 years) and more often female. Classical CV risk factors (hypertension, diabetes, hypercholesterolemia and smoking) were more frequent in T1MI (Table 1).

Prior atherosclerotic CV diseases including CAD, stroke and PAD were similar for both types of MI. T2MI patients had more frequent history of HF or LV dysfunction (8.1 vs 2.1%, $p = 0.025$). Prior AF/flutter (8.1%) or AF/flutter on admission ECG (16.1%) were much more common in T2MI ($p < 0.001$). CAD characteristics at coronary angiography are presented in Figure 2. Compared to T1MI, T2MI had less severe CAD with less frequent multivessel disease (37.2% vs 8.1%, $p < 0.001$). However, although younger, almost 42% of T2MI (26/62) had significant coronary stenosis. P2Y12 inhibitors were more likely to be prescribed in T1MI (91.0% vs 72.6%, $p < 0.001$). By contrast, vitamin K antagonists (VKA) were used only in T2MI patients (8.1%, $p < 0.001$) (Table 2).

Acute stressors for T2MI

Acute or chronic etiological factors involved in T2MI pathophysiology are shown in Figure 3. Coronary embolism (24.2%), severe hypertension \pm LVH (22.6%) and tachyarrhythmia (16.1%) were the main triggering factors. Anemia was infrequently involved (6.4%).

In-hospital outcomes

In-hospital event rates were low in both MI types. In agreement with history and ECG findings, AF/flutter and stroke showed only a non-significant trend toward higher rate in T2MI. Overall hospital mortality was 2.3%. All deaths were from cardiovascular causes. Although the difference was non-significant, death rates in T1MI tended to be higher than in T2MI, as well as occurrence of MACE (Table 3).

DISCUSSION

To the best of our knowledge, this study is the first to investigate the characteristics and in-hospital outcomes of T2MI compared to T1MI in a Sub-Saharan African population. This study is of particular interest for the global perspective of MI and T2MI since there are still many blind spots, particularly for black Africans. We found that the prevalence of T2MI was not exceedingly low (14.1%). In the literature, T2MI incidence varies widely across studies, ranging from 1.6% to 73.8% of MI patients [23]. Retrospective adjudication of MI cases and the recent interest in this topic may explain this relatively low rate. It should also be underscored that differentiating between T1MI, T2MI and even myocardial injury is challenging in daily clinical practice considering the various clinical conditions associated with cTn elevation, potentially leading to misdiagnosis of T2MI [24]. The heterogeneous prevalence of T2MI may also be due

to the difference in the thresholds used, acute triggers, and the definition of oxygen supply/demand mismatch (e.g., supraventricular tachyarrhythmia, anemia...) [23].

Almost all Western studies report that patients with T2MI are older than those with T1MI. The age and comorbidities frequently observed in T2MI patients has resulted in the emergence of a geriatric pathology that includes CAD and additional harmful conditions, which are key determinants of the poor outcomes in these patients [25,26]. Unexpectedly, T2MI patients in our series were slightly younger (by roughly 4 years) than T1MI patients. In addition, T2MI patients were less likely to have the typical cardiovascular risk factors and comorbidities, especially history of CAD. Female predominance was consistent with previous studies [23]. These observations emphasize the wide heterogeneity of this multi-faceted disease. However, there are explanations for some of these differences. As opposed to Western countries, the sub-Saharan population, and particularly in Côte d'Ivoire, is quite young as a result of dynamic population growth and lower life expectancy [27]. Patients with MI are therefore relatively younger than in developed countries, with a 10-year difference [2]. Patients from Côte d'Ivoire included in the REACTIV registry had a mean age of 56 years in the 2010-2016 period (765 patients) [3]. This young population is also characterized by a low rate of comorbidities and cardiovascular risk factors, which gradually increase with age. Nevertheless, this result must be carefully interpreted considering potential variability in sampling, as our study population was quite small. These interesting observations need to be refined and confirmed by multicenter studies on larger populations in sub-Saharan Africa.

The key issues in T2MI that were highlighted in our series are AF/flutter and heart failure, in relation to two predominant triggers (i.e. coronary embolism and AF/flutter). In a systematic review by Wang et al, 9 of the 14 studies included identified arrhythmia, especially tachyarrhythmia, as the main trigger in T2MI [28]. AF is still a diagnostic and therapeutic challenge in sub-Saharan Africa, where the use of anticoagulation and therapeutic efficacy are still below standard in daily practice [29]. Unfortunately, in our study, information about chronic treatments including AF medications was not available. Hypertension and subsequent LVH are also important T2MI triggers. In the multicenter INTERHEART Africa study, hypertension was the most important risk factor associated with a first episode of MI in black Africans (50.4%; OR, 6.99; 95% CI, 4.23–11.55) [30]. Over the last decade, Sub-Saharan Africa has experienced the highest increase of the rate of hypertension, compared to developed countries [31]. Anemia, which is consistent with older age and a frequent comorbidity in the West [16,32], was rarely encountered in our series.

Coronary angiography, performed in all 62 patients with T2MI, highlighted that significant CAD was common in T2MI (41.9%). The rate seen here is lower than in other recent studies, which estimated the prevalence of CAD at > 50% among T2MI patients [33-35]. In contrast with

studies in Western countries, multi-vessel CAD (2-vessel or 3-vessel CAD) was less frequent in T2MI compared to T1MI [33,36]. CAD has emerged as a key prognostic issue in T2MI, and recent data suggest that categorizing T2MI based on the presence or absence of significant CAD [37,38] would improve the characterization T2MI as a clinical entity. This classification is supported by the strong prognostic value of CAD in T2MI [34,39]. Recent findings from the French RICO survey showed that one-year all-cause mortality was dramatically increased, by 40%, in T2MI with significant CAD compared with T1MI patients, after adjustment for confounding factors (HR 1.362; 95%CI 1.029-1.802) [35].

In our study, while in-hospital mortality was low overall, it was lower in T2MI (1.6%) than in T1MI (2.4%). Data on short-term mortality in T2MI are controversial. Although T2MI is often associated with higher in-hospital cardiovascular and all-cause mortality, some studies found no significant difference between T2MI and T1MI [40,41]. Hospital deaths in T2MI could relate to the underlying mechanism of onset, seeing as anemia, hypoxia or hypotension were associated with a worse prognosis [42]. These etiological factors were rarely seen in our population.

Study strength and limitations

Our study has some limitations. First, our sample size was relatively small compared to some Western T2MI registries. As only patients admitted to an ICU were included, selection bias may be induced. Only patients who underwent coronary angiography were included, and the relatively high proportion of excluded patients (87/541, i.e. 16.1%) may have led to bias in the prevalence of T1MI and T2MI and the related data. In the absence of coronary imaging in some T1MI cases (17.1%), the atherothrombotic mechanism defining T1MI could not be confirmed. Distinction between T1MI, T2MI and myocardial injury is a clinical challenge. Only patients with MI diagnosed on the basis of clinical, imaging, or ECG signs, as defined by the current UDMI, were included in this study. Despite this challenge, herein, the T2MI diagnosis was based on current guidelines and was made by two experienced cardiologists with a good inter-observer agreement. Cut-offs used to identify acute triggers for supply-demand oxygen mismatch in T2MI are not standardized to date, and therefore can not be generalized, given the high variability of individuals ischemic thresholds. The management of MI patients is still a challenge in Cote d'Ivoire, as there is a wide gap between quality of care in sub-Saharan Africa and Western countries, mainly demonstrated by prolonged time to admission and scarcity of specialized cardiology units.

Some specific explorations were not performed. Spasm provocation test with ergonovine was not done to confirm coronary vasospasm, nor was the index of microcirculatory resistance to identify microvascular dysfunction. In MI cases with normal coronary arteries or non-significant

CAD, magnetic resonance imaging is of particular interest, but this test was not performed in our study.

Nevertheless, this study is the first to assess, in a sub-Saharan Africa population, characteristics and in-hospital outcomes of T2MI patients compared to T1MI. It therefore adds key data in the understanding of T2MI.

CONCLUSION

Our study, conducted over a 5-year period at the Abidjan Heart Institute, showed significant disparities in the clinical characteristics, angiographic features, etiological framework, and in-hospital outcomes of T2MI compared to Western studies. These results suggest the wide heterogeneity in the etiological characteristics of T2MI according to the epidemiological profile, risk factors and health access of a population. Given the young age of T2MI patients in sub-Saharan Africa, these novel findings challenge the hypothesis of a geriatric pathology. There is thus an urgent need for prospective multicentric studies in this region to confirm our preliminary findings and to assess long-term prognosis.

ARTICLE INFORMATION

Affiliations

Abidjan Heart Institute, Abidjan, Côte d'Ivoire (H.Y., C.T., A.E., E.S., R.N.); PEC2, EA 7460, UFR Health Sciences, University of Bourgogne Franche Comté, Dijon, France (H.Y., M.Z., A.P.); Cardiology department, University Hospital Center Dijon Bourgogne, Dijon, France (Y.C.); Internal Medicine Department, Mont Blanc Hospital, Sallanches, France (A.P.).

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Declaration of conflicting interests

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The other authors have nothing to declare.

Data availability statement

Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

HY: Writing – original draft, Formal analysis; CT: Data curation, Visualization; AE: Validation, ES: Investigation, YC: Methodology, MZ: Conceptualization, Funding, AP: Writing – Review and editing; RN: Supervision, Project administration.

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Figure legend

Figure 1. Flow chart of the study

MI: myocardial infarction.

Figure 2. Severity of coronary artery disease according to type 1 and type 2 myocardial infarction

T1MI: type 1 myocardial infarction. T2MI: type 2 myocardial infarction.

Figure 3. Pathophysiological mechanisms of type 2 myocardial infarction.

LVH: left ventricular hypertrophy. SCAD: spontaneous coronary artery dissection.

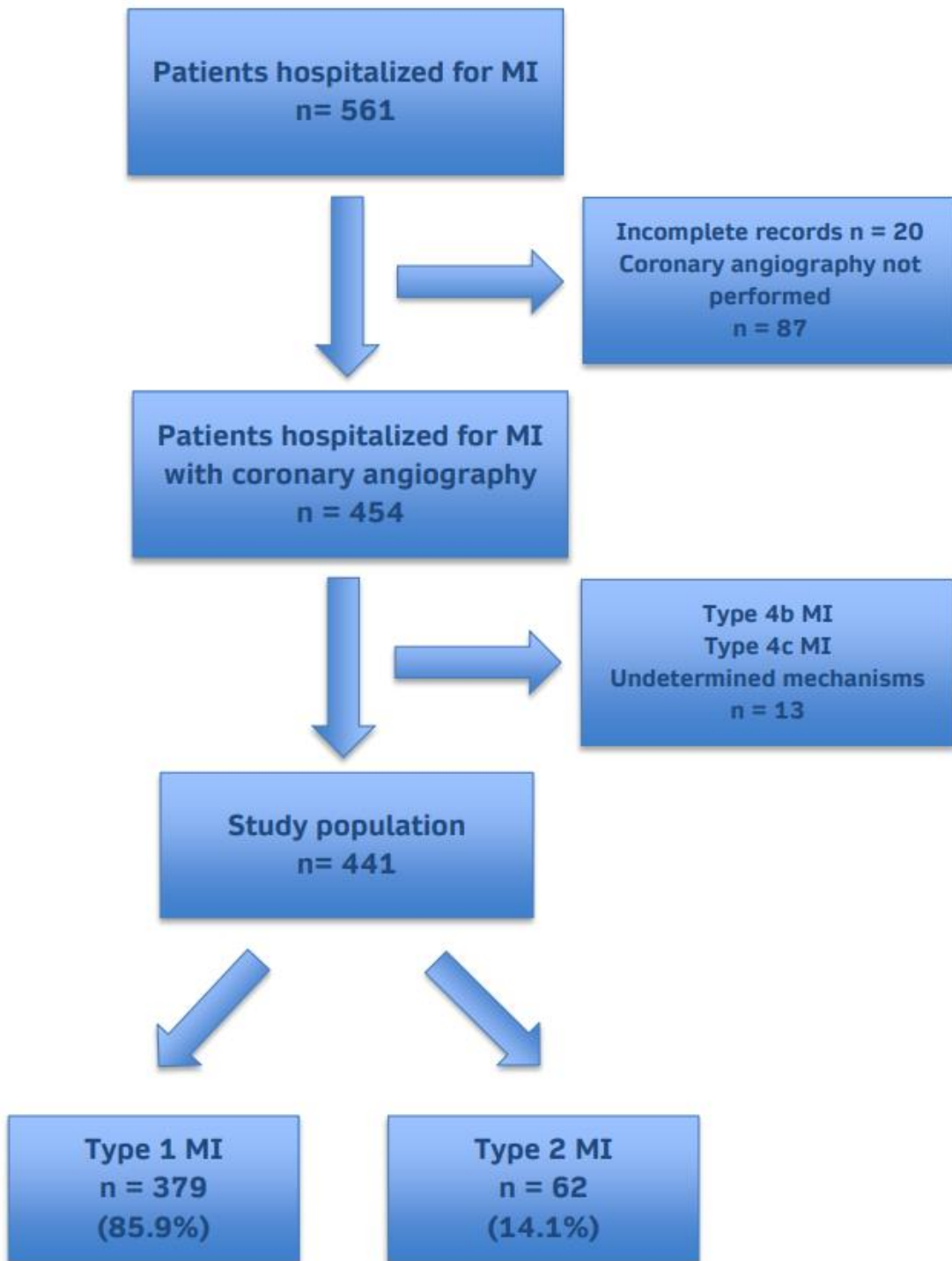


Figure 1.

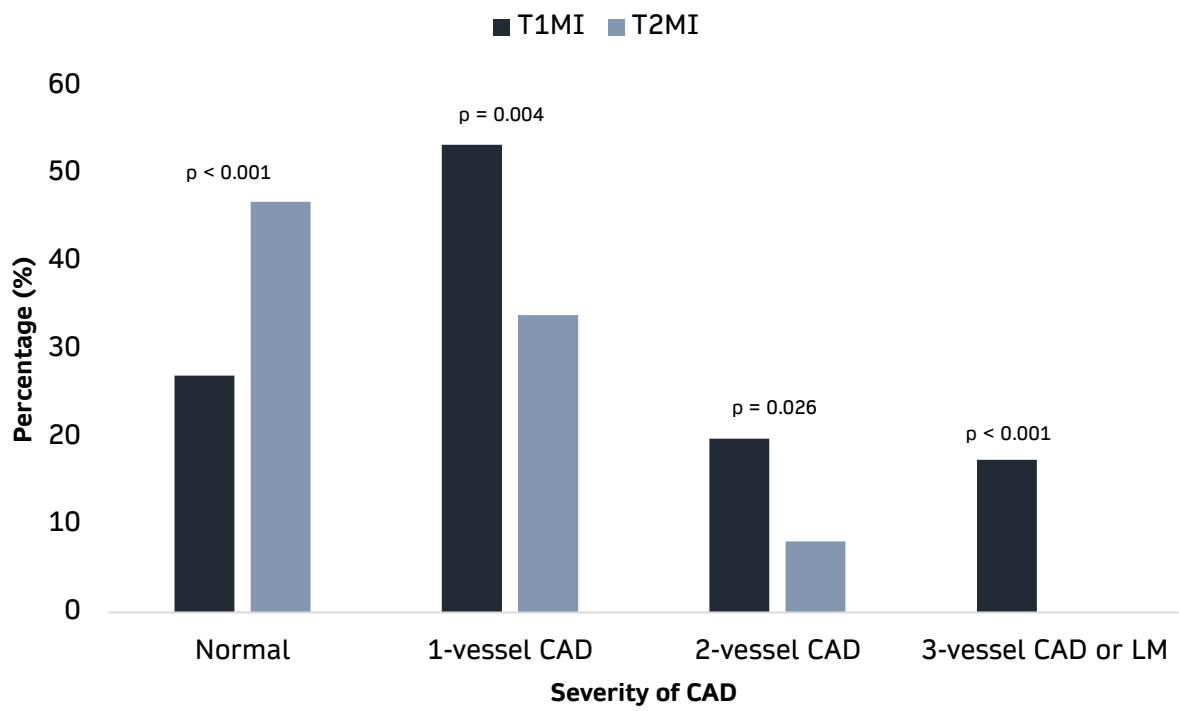
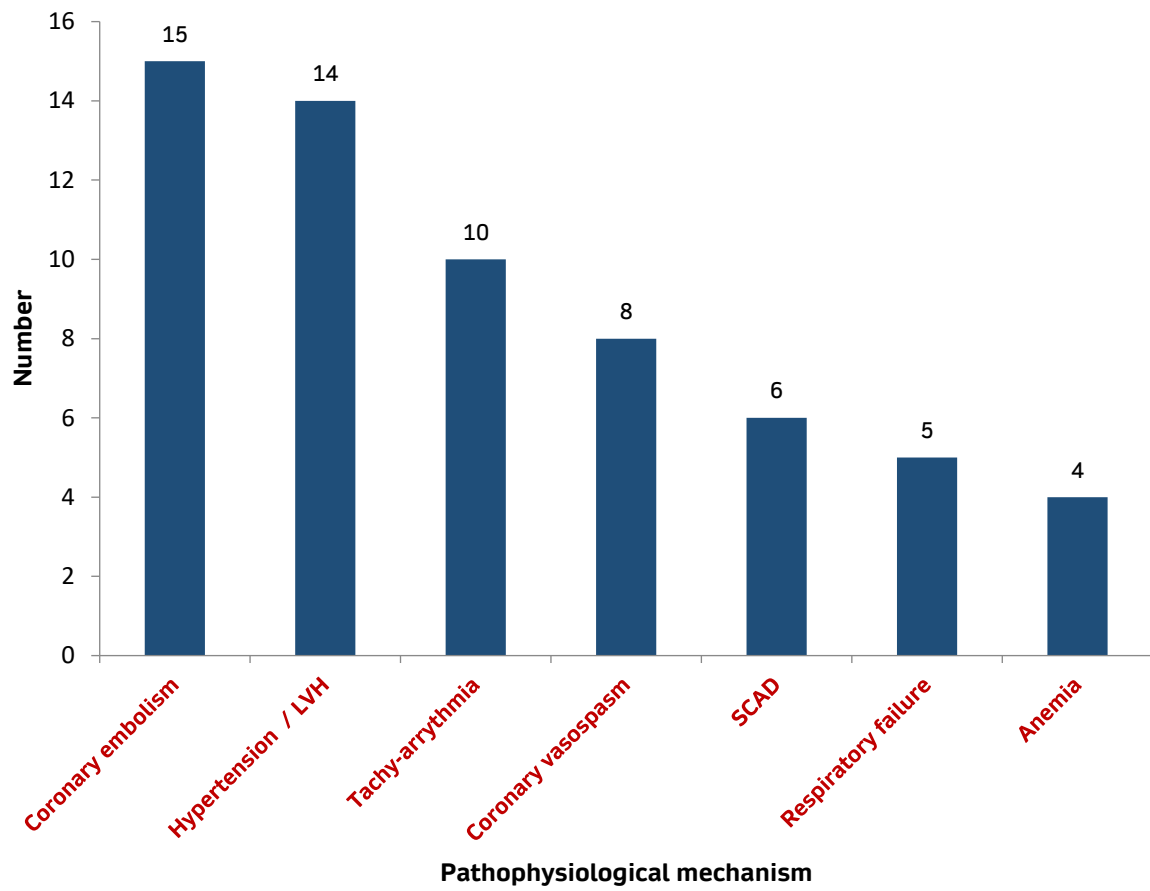


Figure 2.



LVH : left ventricular hypertrophy. SCAD : spontaneous coronary artery dissection.

Figure 3.

Table 1. Patients characteristics (n(%) or median [IQR] or mean \pm standard deviation).

Parameters	T1MI n = 379	T2MI n = 62	p
Risk factors and comorbidities			
Age, years	58 [50-65]	54 [43-64]	0.091
Female	75 (19.8)	20 (32.3)	0.031
Hypertension	232 (61.2)	36 (58.1)	0.675
Diabetes	110 (29.0)	10 (16.1)	0.044
Hypercholesterolemia	111 (29.3)	14 (22.5)	0.362
Smoking	92 (24.3)	9 (14.5)	0.090
Family history of CAD	17 (4.5)	0 (0)	0.147
BMI, kg/m^2	27.4 [23.9-30.4]	25.7 [22.1-28.3]	0.045
Obesity	87 (22.9)	10 (16.1)	0.229
Cardiovascular history			
MI	32 (8.4)	2 (3.2)	0.202
PCI	14 (3.7)	0 (0)	0.235
Stroke	21 (5.5)	3 (4.8)	0.556
PAD	12 (3.2)	1 (1.6)	1.000
Heart failure/ LV dysfunction	8 (2.1)	5 (8.1)	0.025
AF / flutter	1 (0.3)	5 (8.1)	< 0.001
Clinical data			
Onset of symptoms-admission, <i>hours</i>	20 [7-72]	26 [5-93]	0.593
Killip admission \geq 2	79 (20.8)	12 (19.4)	0.788
SBP, <i>mmHg</i>	140 [127-161]	135 [112-158]	0.055
DBP, <i>mmHg</i>	90 [80-102]	87 [71-100]	0.190
HR, <i>beats/min</i>	83 [71-99]	84 [71-97]	0.722
ECG at admission			
STEMI	256 (67.5)	38 (61.3)	0.332
Anterior wall MI	195 (51.4)	22 (35.5)	0.020
AF/Flutter	4 (1.1)	10 (16.1)	< 0.001
Echocardiography			
LVEF, %	53 [44-61]	55 [42-60]	0.793
LVEF \leq 40%	59 (15.6)	14 (22.6)	0.168
Biology			
Hemoglobin, g/100mL	13.7 [12.3-15.0]	13.6 [12.2-15.0]	0.756
CRP, mg/L	23.3 [5.4-89.0]	15.3 [4.5-75.0]	0.189
CRP \geq 6 mg/L	119 (31.4)	24 (38.7)	0.254
Creatinine, mg/L	12.1 [10.0-14.7]	12.4 [9.7-15.9]	0.868
eGFR, mL/min/1.73m ²	74.9 [57.9-93.7]	69.0 [52.7-89.6]	0.624
hs Troponin I peak, ng/L	3416 [552-25470]	2113 [2210-18348]	0.084
NT-proBNP, pg/mL	1663 [518-5013]	1559 [491-5055]	0.956
Length of stay in ICU, days	3 [2-4]	3 [2-4]	0.530

T1MI: type 1 myocardial infarction. T2MI: type 2 myocardial infarction. CAD: coronary artery disease. BMI: body mass index. MI: myocardial infarction. PCI: percutaneous coronary intervention. PAD: peripheral arterial disease. LV: left ventricular. AF: atrial fibrillation. SBP: systolic blood pressure. DBP: diastolic blood pressure. HR: heart rate. STEMI: ST-segment elevation myocardial infarction. MI: myocardial infarction. VT: ventricular tachycardia. AVB: atrioventricular block. LVEF: left ventricular ejection. CRP: C-reactive protein. eGFR: estimated Glomerular Filtration Rate. hs: high sensitivity. NT-proBNP: N-Terminal pro Brain Natriuretic Peptide. ICU: intensive care unit.

Table 2. In-hospital management (n(%)).

Acute treatments	T1MI n = 379	T2MI n = 62	p
Thrombolysis	40 (10.5)	9 (14.5)	0.357
PCI	168 (44.3)	12 (19.3)	< 0.001
Aspirin	356 (93.9)	54 (87.1)	0.061
P2Y12 inhibitors	345 (91.0)	45 (72.6)	< 0.001
Unfractionated heparin	28 (7.4)	13 (21.0)	< 0.001
LMWH	308 (81.3)	40 (64.5)	0.002
Beta blockers	273 (72.0)	40 (64.5)	0.226
Statins	287 (75.7)	45 (72.6)	0.594
ACEI/ARB	271 (71.5)	44 (71.0)	0.931
Diuretics	96 (25.3)	20 (32.2)	0.250
DOA	0 (0)	1 (1.6)	0.140
VKA	0 (0)	5 (8.1)	< 0.001

PCI : percutaneous coronary intervention. LMWH: low molecular weight heparin. ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin 2 receptor blocker. DOA: direct oral anticoagulant. VKA: vitamin K antagonist.

Table 3. In-hospital events.

Variables	T1MI n = 379	T2MI n = 62	p
Heart failure	15 (3.9)	3 (4.8)	0.728
Sustained VT	12 (3.2)	3 (4.8)	0.453
AF / flutter	2 (0.5)	1 (1.6)	0.093
Transfusion or major bleeding	4 (1.0)	3 (4.8)	0.061
Stroke	3 (0.8)	2 (3.2)	0.147
Death	9 (2.4)	1 (1.6)	0.104
MACE	18 (4.7)	2 (3.2)	1.000

T1MI: type 1 myocardial infarction. T2MI: type 2 myocardial infarction. VT: ventricular tachycardia. AF: atrial fibrillation. MACE: major adverse cardiac events.

3.3. Rôle de la maladie coronaire dans l'infarctus du myocarde de type 2

Cette dernière partie s'est attachée à mieux comprendre le rôle de la pathologie coronaire dans l'IDM de type 2. En effet, parmi les patients présentant un IDM de type 2, les travaux notamment issus de notre groupe ⁴⁸, ont souligné que la présence d'une maladie coronaire obstructive était fréquente, et elle représente de forts enjeux pronostiques et thérapeutiques. La maladie coronaire semble également insuffisamment traitée chez les patients atteints d'IDM de type 2, alors que le l'opportunité et le timing de la réalisation des procédures interventionnelles reste discuté. Dans cette revue de la littérature, nous avons donc analysé la prévalence et la sévérité de la coronaropathie sous-jacente dans l'IDM de type 2, les éléments de la discrimination entre IDM de type 1 et de type 2 en présence d'une coronaropathie obstructive, et la valeur pronostique de la maladie coronaire obstructive chez les patients atteints d'IDM de type 2.

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Coronary artery disease: a key issue in type 2 myocardial infarction: systematic review and recent findings

Hermann Yao ^{1,2,*}, Marianne Zeller ¹, Roland N'Guetta ², Yves Cottin ³ and Alain Putot ⁴

¹ PEC2, EA 7460, UFR Health Sciences, University of Bourgogne Franche Comté, Dijon, France; Marianne.Zeller@u-bourgogne.fr

² Abidjan Heart Institute, 01 BPV 206 Abidjan, Côte d'Ivoire; rolandnguetta@hotmail.com

³ Cardiology department, University Hospital Center Dijon Bourgogne, 21000 Dijon, France; yves.cottin@chu-dijon.fr

⁴ Internal Medicine Department, Mont Blanc Hospital, 74703 Sallanches, France; A.Putot@ch-sallanches-chamonix.fr

Correspondence: hermannyao@gmail.com

Abstract: Underlying coronary artery disease (CAD) is increasingly considered to be a key issue in the pathophysiology of type 2 myocardial infarction (T2MI). In T2MI, which is attributable to mismatch between oxygen supply/demand, CAD is common and appears to be more severe than in type 1 myocardial infarction (T1MI). Little is known about the heterogeneous mechanisms that cause supply/demand imbalance and non-coronary triggers leading to myocardial ischemia or about how they are potentially modulated by the presence and severity of CAD. CAD seems to be underrecognized and undertreated in T2MI, even though previous studies have demonstrated both short and long-term prognostic value of CAD in T2MI. In this literature review, we attempt to address the prevalence and severity of CAD, challenges in the discrimination between T2MI and T1MI in the presence of CAD, and the prognostic value of CAD among patients with T2MI.

Keywords: type 2 myocardial infarction; coronary angiography; coronary artery disease; prognosis; secondary prevention medications.

1. Introduction

Type 2 myocardial infarction (T2MI) remains an enigmatic clinical entity, and there are still many uncertainties regarding diagnostic and prognostic criteria, biomarkers for ischemia, the ischemic threshold, the role of cardiac imaging, and management strategies [1]. Although considered to be a cornerstone of prognosis and targeted treatment strategies, underlying coronary artery disease (CAD) is often unrecognized and undertreated in T2MI [2]. Thus, a better understanding of this ambiguous entity, and especially the role of CAD, is of particular interest [2]. The clinical classification of T2MI was introduced in 2007 [3] and redefined in 2012 [4]. The most recent revision was for the fourth universal definition of MI (UDMI) in 2018 [5]. A diagnosis of T2MI is based on criteria for myocardial infarction (MI), with evidence of an imbalance between myocardial oxygen supply and demand and in the absence of atherothrombosis. T2MI is the consequence of three interrelated factors: (1) vascular aging, including atherosclerosis; (2) predisposing chronic cardiac and extra-cardiac conditions and (3) ischemic triggers [5,6]. A wide range of conditions often encountered in the management of geriatric patients can lead to T2MI [4,7,8,9]. In 2019, de Lemos proposed a redefinition of T2MI and Type 1 MI (T1MI) derived from the fourth UDMI, considering both the underlying pathophysiological mechanisms and the management of T2MI [10]. The authors proposed that some subtypes based on pathophysiological mechanisms and management move from T2MI toward T1MI. These subtypes include spontaneous coronary artery dissection, coronary embolism, and vasomotor abnormalities. Moreover, in this proposal, CAD was the core of the clinical issue, as T2MI was categorized into two sub-groups based on the presence/lack of obstructive CAD, with $\geq 50\%$ stenosis in at least one coronary vessel [10]. There are major therapeutic implications related to the subclassification of T2MI according to the presence or absence of significant CAD because subsequent management approaches differ substantially. Moreover, although prognostic studies on CAD in T2MI are scarce, they suggest a potent predictive value [11,12].

Based on a systematic review of the literature, we aimed to describe the prevalence, diagnosis, prognosis, and management of CAD in T2MI.

2. Materials and Methods

For this review, we identified all English language studies assessing CAD in T2MI patients published between 2012 and 2022 using the MEDLINE database (PubMed; National Library of Medicine, NIH, Bethesda, MD, USA) in accordance with PRISMA standards [13] (Figure 1). The studies are summarized in Table 1 [8,11,12,14,15,16,17,18,19,20,21,22,23,24].

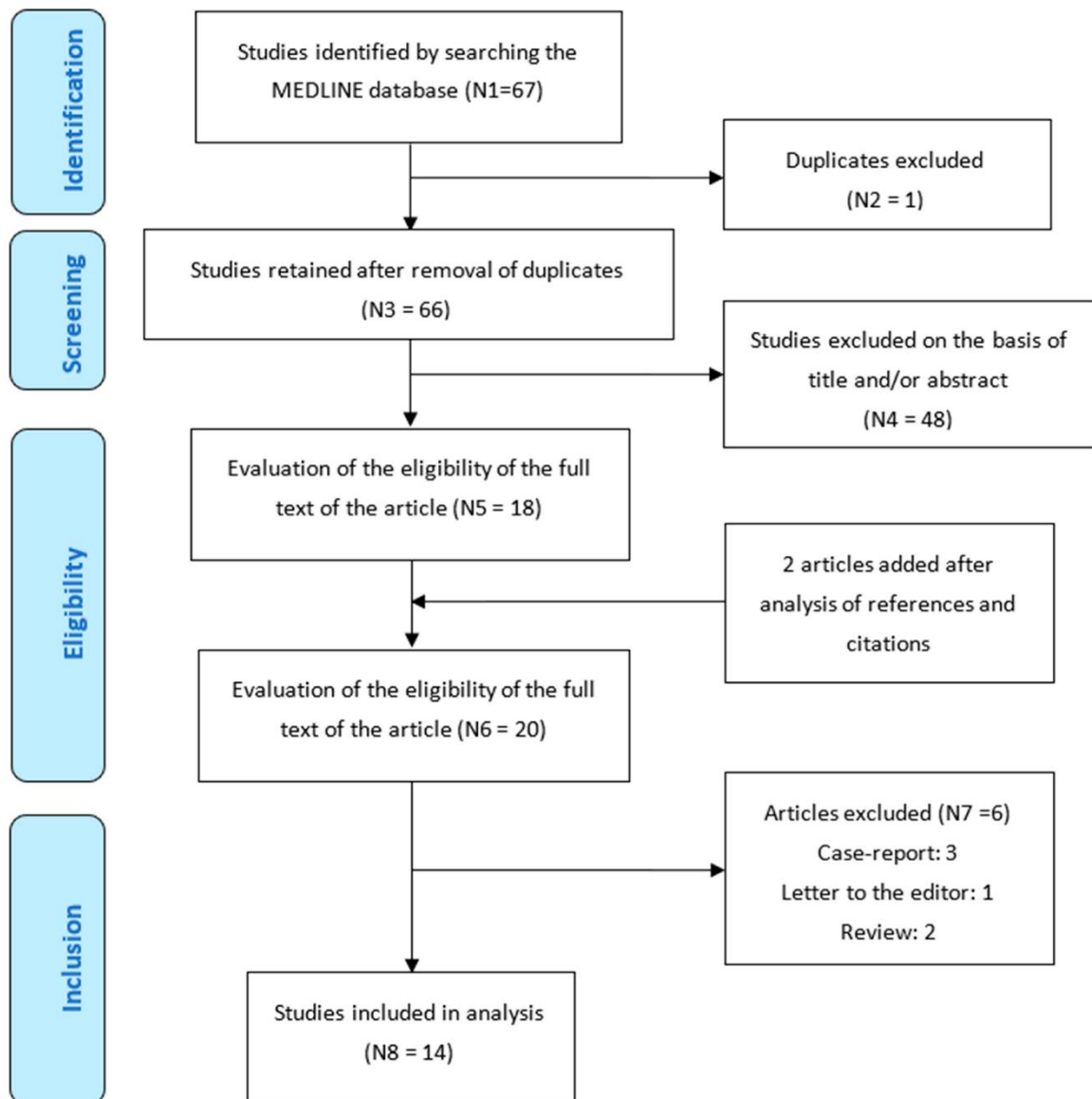


Figure 1: Flow chart of the study.

Table 1. Type 2 myocardial infarction and CAD.

Author (year) (Study name)	Country	Type of study	Objectives	T2MI Patients	Results	Conclusion
Bularga (2022) [13] (DEMAND MI)	Scotland	Prospective study	Prevalence of CAD	93 patients	CAD 68% Obstructive CAD 30%	Unrecognized and untreated CAD is seen in most patients with T2MI
Wereski (2022) [14] (High-STEACS)	Scotland	Multicenter randomized trial	Risk factors for T1MI and T2MI	407 patients	Known CAD is predictor for both T1MI and T2MI	Risk factors for CAD associated with T1MI are also important predictors of T2MI events
Kimnai (2021) [15] (SWEDEHEART)	Sweden	Prospective registry	Sex differences in characteristics and outcomes in patients with T2MI	6485 patients	Obstructive CAD: 34% (women) vs 67% (men) History of CAD was associated with all-cause death in women (HR 1.26; 95%CI 1.08-1.47)	Women with T2MI are less likely to have obstructive CAD than men Need for a sex-specific approach management of T2MI
Putot (2020) [23] (RICO)	France	Prospective registry	Characteristics and underlying causes of T2MI	862 patients	Obstructive CAD: 63% of T2MI CAD was not associated with T2MI versus T1MI (HR 1.03; 95%CI 0.96-1.12)	Although frequent among T2MI patients, CAD was not associated with T2MI diagnosis in multivariate analysis
Putot (2019) [16] (RICO)	France	Prospective registry	CAD as predictive factor for distinguishing T2MI / T1MI	873 patients	History of CAD 29 %	Previous CAD was associated with a 40% higher risk of T2MI
Putot (2018) [17] (RICO)	France	Cross-sectional study	Predictors for in-hospital all-cause and cardiovascular mortality	947 patients	CAD is not associated with in-hospital mortality among T2MI patients	Independent predictors for CV mortality: age >75 years, initial hemodynamic parameters and troponin level rate at admission Predictors for all-cause mortality: initial hemodynamic parameters, creatinine, troponin, and CRP
Chapman (2018) [11]	Scotland	Prospective study	Predictor for poor outcomes among patients with T2MI or myocardial injury	429 patients	CAD was independent predictor for MACE in patients with T2MI or myocardial injury (HR, 1.71; 95%CI 1.31-2.24).	Identification of CAD in T2MI patients may help target therapies that could modify future risk.
Gaggin (2017) [18] (CASABLANCA)	USA	Single-center prospective study	Incident T2MI	152 patients	History of CAD 71% $\geq 50\%$ 2-vessel CAD 61.2% $\geq 70\%$ 2-vessel CAD 47.7%	History of CAD is predictor for first T2MI

Neumann (2017) [19] (BACC)	Germany	Prospective	Discrimination of patients with T2MI	99 patients	History of CAD 29.3% Obstructive CAD 39.5% 3-vessel CAD 21.1%	CAD was not a strong predictor to discriminate T1MI and T2MI
Baron (2016) [12] (SWEDEHEART)	Sweden	Prospective registry	Characteristics and long-term prognosis in T2MI and T1MI patients with and without obstructive CAD	1316 patients	T2MI with CAD: 52.8% Higher crude long-term mortality in T2MI with CAD (HR 1.72; 95% CI 1.45-2.03)	Evaluation of coronary artery status seems to have a key role in choice of treatment and risk prediction.
Radovanovic (2016) [20] (AMIS PLUS)	Switzerland	Prospective	Incidence, presentation, treatment and outcome of T2MI	1091 patients	History of CAD 36.8% Obstructive CAD 92.8%	Difference in prevalence of obstructive CAD across studies is probably due to the different definitions of angiographic findings.
López-Cuenca (2016) [21]	Spain	Single-center retrospective study	Comparison of clinical features, treatment strategies and outcomes between T2MI and T1MI	117 patients	Obstructive CAD 33%	Obstructive CAD is more common among T1MI patients
Saaby (2013) [8] (DEF-AMI)	Denmark	Single-center cross-sectional study	Investigate the frequency and features of T2MI	144 patients	Significant CAD: 54.8%	Approximately half of patients with T2MI have significant CAD
Ambrose (2012) [22]	USA	Single-center cross-sectional study	Severity of CAD between T2MI and T1MI	31 patients	Previous CAD : 45.2% 3-vessel CAD : 32.3% (T2MI) vs 26.6% (T1 NSTEMI) and 4.1% (T1 STEMI)	T2MI patients with significant CAD appear to be more severe with more 3-vessel disease compared to patients with T1MI

CAD: coronary artery disease. T2MI: type 2 myocardial infarction. T1MI: type 1 myocardial infarction. STEMI: ST-segment elevation myocardial infarction. NSTEMI: non ST-segment elevation myocardial infarction. HR: hazard ratio. CI: confidence interval. CRP: C-reactive protein. DEMAND-MI: Determining the Mechanism of Myocardial Injury and Role of Coronary Disease in Type 2 Myocardial Infarction. High-STEACS : High-Sensitivity Troponin in the Evaluation of patients with Acute Coronary Syndrome. SWEDEHEART: Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. RICO: Observatoire des Infarctus de la Côte d'Or. CASABLANCA: Catheter Sampled Blood Archive in Cardiovascular Diseases. BACC: Biomarkers in Acute Cardiac Care. AMIS PLUS : national Registry of Acute Myocardial Infarction in Switzerland. DEF-AMI: consequences of the universal 2007 DEfinition of Acute Myocardial Infarction studied in a Danish consecutive hospital population.

3. T2MI Criteria for Diagnosis

Acute MI is currently defined based on the fourth UDMI [5]. T2MI was defined as MI secondary to myocardial oxygen supply/demand imbalance and triggered by an acute stressor. These conditions are defined in Table 2 [4,7,8,9,25].

Table 2. Definition criteria of acute stressors in type 2 myocardial infarction.

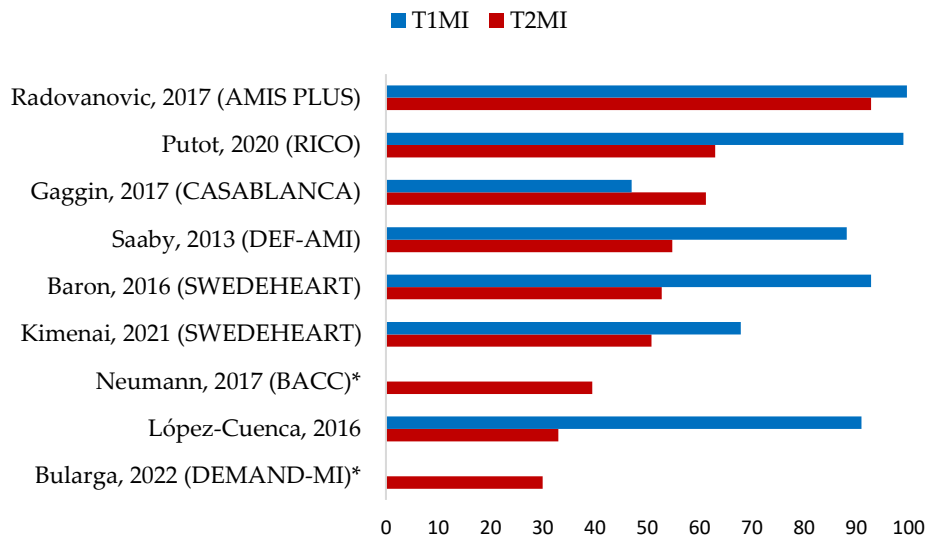
Mechanism	Definition
Sustained tachy-arrhythmia [8]	supraventricular tachy-arrhythmia \geq 20 min with a ventricular rate >150 beats/min
Severe hypertension [8]	systolic blood pressure > 160 mmHg, with or without concomitant LVH identified by echocardiography
Severe brady-arrhythmia [8]	brady-arrhythmia requiring medical treatment or pacing
Respiratory failure [9]	clinical signs of acute respiratory distress lasting \geq 20 minutes and arterial oxygen tension < 8 kPa
Severe anaemia [8]	hemoglobin concentration < 5.5 mmol/L for men and < 5.0 mmol/L for women (measured on admission) and/or the need to use blood products
Hypotension/shock [25]	systolic BP < 90 mmHg and/or diastolic BP < 60 mmHg associated with evidence of systemic hypo-perfusion (e.g. hyperlactatemia) and low cardiac output.
Spontaneous coronary artery dissection [7]	was defined as spontaneous dissection of the coronary artery wall with accumulation of blood within the false lumen, which can compress the true lumen to varying degrees
Coronary spasm [4]	refers to a sudden, intense vasoconstriction of an epicardial coronary artery that causes vessel occlusion or near occlusion on coronary angiography, even in the absence of stimulation
Coronary embolism [8]	defined as a high thrombus burden despite a relatively normal underlying vessel or recurrent coronary thrombus (left heart endocarditis, intracardiac mural thrombus, documented venous thrombus, and a patent foramen ovale or atrial septum defect)

LVH: left ventricular hypertrophy. BP: blood pressure.

4. Prevalence and Severity of CAD in T2MI Based on Coronary Angiography

CAD has been presented as an important determinant in T2MI categorization. Moreover, fixed stable coronary atherosclerosis, as a promoter of myocardial oxygen balance mismatch, is a key factor in T2MI pathophysiology [5]. Obstructive atherosclerosis is a common condition in T2MI patients who undergo coronary angiography, with a prevalence ranging from 30% to 68% [14] (Figure 2). In the nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDHEART) registry, CAD accounted for 57.6% of cases among patients with T2MI [12]. In the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) study [19], coronary angiography was performed in 152 included T2MI patients, of whom 61.2% had two-vessel disease ($\geq 50\%$ stenosis).

Figure 2. Prevalence of significant coronary artery disease ($\geq 50\%$) according to type 1 and type 2 myocardial infarction patients undergoing coronary angiography (%)



T1MI: type 1 myocardial infarction. T2MI: type 2 myocardial infarction. AMIS PLUS : national Registry of Acute Myocardial Infarction in Switzerland; CASABLANCA : Catheter Sampled Blood Archive in Cardiovascular Diseases; DEF-AMI: consequences of the universal 2007 DEFinition of Acute Myocardial Infarction studied in a Danish consecutive hospital population; SWEDEHEART: Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies; BACC: Biomarkers in Acute Cardiac Care; DEMAND-MI: Determining the Mechanism of Myocardial Injury and Role of Coronary Disease in Type 2 Myocardial Infarction.

* non applicable for T1MI

However, variations in the prevalence of CAD partly depend on the rates of patients who undergo coronary angiography. A recent meta-analysis by White et al [26] included 40 cohort studies with 13,803 T2MI patients and 98,930 T1MI patients. T2MI patients were less likely to undergo coronary angiography (OR 0.09; 95%CI 0.06–0.12), leading to an underestimation of the true prevalence of CAD. When compared with T1MI, T2MI patients are usually older, with higher rates of comorbidities, so angiographic explorations tend to be less frequent. In a large multicenter randomized clinical trial testing the implementation of a high-sensitivity-cardiac Troponin I (hs-cTn I) assay and UDMI recommendations in consecutive MI patients in Scotland, only 10% of T2MI patients underwent angiography compared to 59% of T1MI patients [27]. In a cross-sectional study from the 2018 National Inpatient Sample in the USA, including 268,850 patients admitted for T2MI, only 11.2% of T2MI were managed invasively, of which only 17.9% underwent coronary revascularization. There are wide disparities in the rate of coronary angiography use, mainly related to insurance status and geographic regions and independent of patient and hospital factors [28]. When compared with conservative management and after propensity-matched analyses, invasive management reduced in-hospital mortality by 30% in T2MI patients (OR 0.70; 95%CI, 0.59–0.84) [28].

Moreover, thresholds used for identifying obstructive CAD during angiography vary across studies, thus influencing the rate of patients with CAD. In a recent meta-analysis, obstructive CAD was found in 34% of T2MI cases, with the definition of coronary vessel narrowing

varying between 50 and 70% [26]. In the CASABLANCA study, almost half of T2MI patients (47.7%) had $\geq 70\%$ stenosis in at least two vessels, and 61.2% had $\geq 50\%$ stenosis [19]. Among T2MI patients, the presence and severity of CAD can also differ according to sex, as women are less likely to have obstructive CAD than men (34% vs. 67%, respectively) [16].

Another key issue is that underlying CAD has been shown to be more severe in T2MI than in T1MI [17,19,23]. In patients admitted to the emergency department (ED) with a history of CAD, those with T2MI are more likely to have left main or three-vessel disease (with $\geq 50\%$ stenosis) (56% of T2MI vs. 43% of T1MI, $p = 0.015$) [17]. In the CASABLANCA study, a higher CAD burden in T2MI was observed no matter the threshold used to define significant stenosis. Compared to T1MI, the rate of three-vessel disease in T2MI was higher for all thresholds, i.e., $\geq 30\%$ stenosis (57.4% vs. 42.8%, $p = 0.002$), $\geq 50\%$ stenosis (41.1% vs. 27.1%, $p = 0.001$), and $\geq 70\%$ stenosis (25.0% vs. 16.6%, $p = 0.02$) [19].

In most studies, classical CV risk factors are frequently associated with T2MI and CAD [29]. Beyond these classical risk factors, non-conventional risk factors such as depression can also contribute to the pathogenesis of CAD, particularly in T2MI [30].

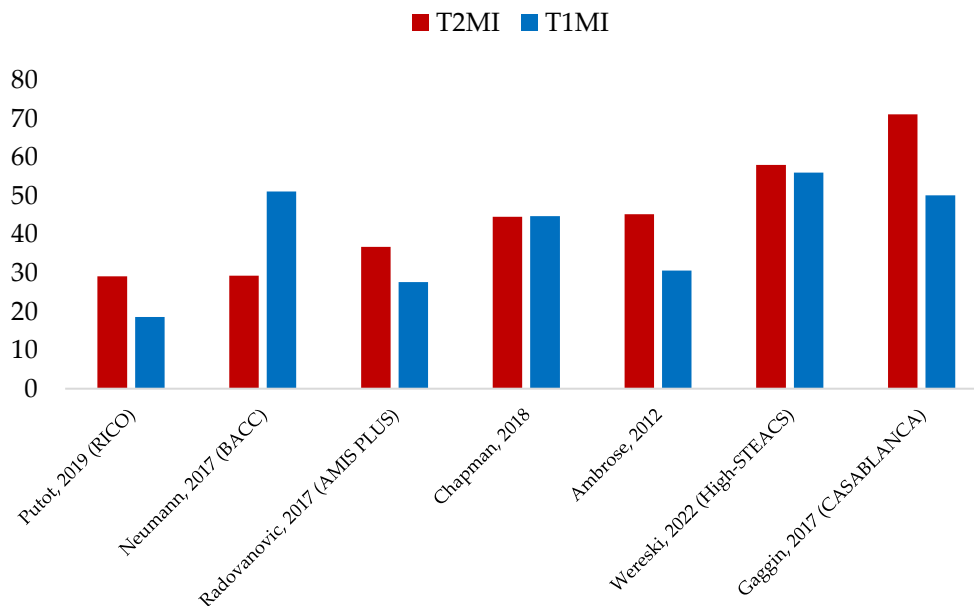
5. Diagnostic Methods for Detecting CAD in T2MI

Coronary angiography remains the gold standard technique for detecting CAD in both T1MI and T2MI. Although T2MI diagnosis is based on myocardial oxygen mismatch in the absence of atherothrombosis, plaque disruption or intracoronary thrombus are not exclusive to T1MI, leading to confusion regarding the diagnostic criteria to be considered [31]. Indeed, coronary angiography and intravascular ultrasound imaging (IVUS) findings showed plaque rupture in patients with MI (33% of cases) as well as in stable (11%) and asymptomatic CAD patients (11%) [32]. An ongoing randomized trial is expected to provide more comprehensive data on the appropriateness of coronary investigations in patients with T2MI [33]. In addition to coronary angiography, cardiac magnetic resonance (CMR) imaging could help discriminate between MI types. In a study among 100 patients with T2MI, systematic coronary and CMR imaging led to the reclassification of seven patients to T1MI and myocardial injury [14]. It is important to note that differentiating between T1MI, T2MI, and even myocardial injury is often a clinical challenge because of the various differential diagnoses associated with cTn elevation, potentially leading to the misdiagnosis of T2MI [34]. The diagnostic and prognostic value of CMR is of particular interest in patients with a working diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) [35,36]. Both a CMR-confirmed diagnosis of MINOCA and a myocardial extension of late gadolinium enhancement are associated with an increased risk of major adverse cardiovascular events at follow-up [35,36]. Coronary computed tomography angiography (CCTA), often used as a rule-out strategy in patients with inconclusive tests, helps identify the presence of obstructive or non-obstructive plaque and guides preventative medical therapies [37]. In patients with normal coronary arteries, non-obstructive coronary disease, or distal obstructive disease, invasive imaging is not required [38]. Finally, stress echocardiography and global longitudinal strain on resting echocardiography may sometimes be useful to identify CAD [39].

6. History of CAD in T2MI and Clinical Implications

A history of CAD, i.e., medically documented CAD, is another way to address CAD. T2MI patients frequently have a history of CAD, apparently more often than T1MI patients, with rates beyond 70% in the CASABLANCA study [19,24,40] (Figure 3). However, recent data from the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients with Suspected Acute Coronary Syndrome) study suggested similar rates of known CAD among patients with T1MI or T2MI (56% vs. 58%, respectively) [15]. In patients admitted to the ED, CAD history was an independent predictive factor for T2MI versus T1MI, increasing the risk by almost 40% (OR 1.38; 95%CI 1.08–1.77) [17]. Finally, the history of CAD in T2MI has an important CV prognostic value because it increases the risk for both T1MI (aHR 1.34, 95%CI 1.28–1.42) and T2MI (aHR 1.11, 95%CI 1.07–1.16) at one year of follow-up [15].

Figure 3: Prevalence of history of coronary artery disease according to type 1 and type 2 myocardial infarction (%)



T1MI: type 1 myocardial infarction; T2MI: type 2 myocardial infarction; RICO: ObseRvatoire des Infarctus de la Côte d’Or; BACC: Biomarkers in Acute Cardiac Care; RICO: obseRvatoire des Infarctus de la Côte d’Or ; AMIS PLUS : national Registry of Acute Myocardial Infarction in Switzerland; High-STEACS : High-Sensitivity Troponin in the Evaluation of patients with Acute Coronary Syndrome ; CASABLANCA : Catheter Sampled Blood Archive in Cardiovascular Diseases.

7. Discrimination of T2MI vs. T1MI in the Presence of CAD: Role of Biomarkers

In the absence of specific biomarkers, differentiation between T1MI and T2MI is based on clinical criteria [5], but it can be difficult to make a differential diagnosis in some situations. Surprisingly, in a relatively small sample of T2MI patients, Bularga et al. showed a slightly higher peak of hs-cTn I in patients without CAD vs. with CAD on cardiac imaging (magnetic

resonance or echocardiography) [14]. When comparing patients with previous CAD in T1MI and T2MI, T2MI had higher CRP levels, whereas T1MI patients had a cTn peak approximately eight times higher; the CRP/Tn I ratio had the best predictive values with an area under the curve (AUC) of 0.84 (95%CI: 0.81–0.87) to discriminate between T2MI and T1MI [17].

Interestingly, underlying CAD in T2MI patients has been associated with preferential triggering mechanisms. Tachyarrhythmia and acute anemia/bleeding were more likely to occur in T2MI with CAD, while respiratory insufficiency was more prevalent in T2MI without CAD [12]. Further studies are needed to address this gap in knowledge on the underlying pathophysiology of T2MI and to elucidate how CAD burden could promote acute myocardial oxygen balance mismatch in patients with tachyarrhythmia or acute anemia related to severe bleeding.

In T2MI, the myocardial oxygen supply/demand imbalance attributable to acute myocardial ischemia is often multifactorial. It can be related to reduced myocardial perfusion due to fixed coronary atherosclerosis without plaque rupture in large vessel stenosis and to coronary microvascular dysfunction, including endothelial dysfunction, smooth muscle cell dysfunction, and sympathetic innervation dysregulation [5]. Coronary microvascular dysfunction is a major cause of myocardial ischemia, is associated with a high risk of poor outcomes, and often associated with CV risk factors such as diabetes [41]. Furthermore, there is a close interaction between microvascular and epicardial CAD, and coronary microvascular dysfunction has been shown to be a strong prognostic factor for patients with and without significant stenosis [42]. Moreover, it has been suggested that microcirculatory dysfunction can be a confounder of CAD in evaluating the hemodynamic status of coronary circulation [43].

8. Prognosis in T2MI Patients with CAD and Treatment Strategies

When compared with T1MI, T2MI is associated with a high rate of mortality, which was found to be more than two-thirds over 5 years, mostly from non-CV causes [11]. However, only a few studies have addressed the prognostic value of CAD among patients with T2MI (Table 2). Among T1MI and T2MI patients with significant CAD (defined as coronary stenosis $\geq 50\%$), in-hospital all-cause mortality risk was increased twofold in T2MI patients (15% vs. 7% for T1MI, $p < 0.001$). However, CV deaths were comparable between the groups [17]. CAD has been shown to have a deleterious long-term impact on T2MI. Among the 41,817 patients with T2MI and T1MI included in the SWEDHEART registry who underwent coronary angiography, T2MI patients with obstructive CAD had higher crude long-term (1.9 years) all-cause mortality than T1MI patients with obstructive CAD (HR 1.72; 95%CI 1.45–2.03) [12] (Table 3). However, after adjustments for confounders, long-term mortality risk was 30% lower in T2MI with obstructive CAD, indicating that factors other than the myocardial infarction itself influence the outcome. It should be noted, however, that coronary angiography was performed in less than one-third of patients, thus limiting the interpretation of these findings. The evidence for the prognostic impact of CAD in T2MI appears to be weak. Previous studies, including patients with MI (without distinction of clinical MI type), found that patients without significant CAD had a better short- and long-term prognosis than patients with

obstructive CAD [44]. In a single-center Scottish cohort of 2122 consecutive patients with elevated cTn [11], a history of CAD was the strongest predictor of major cardiac events after 5 years in patients with T2MI (or myocardial injury) (HR 1.71; 95%CI 1.31–2.24).

Strikingly, when compared with T1MI patients with CAD, patients with T2MI and CAD are dramatically less likely to receive all secondary prevention therapies at discharge, including aspirin (66.2% vs. 90.7%), statins (69.2% vs. 86.0%) or angiotensin-converting enzyme inhibitor (52.9% vs. 71.3%, $p < 0.001$ for all). Moreover, a recent meta-analysis highlighted the lower rate of conventional cardioprotective medications in patients with T2MI (vs. T1MI), including beta blockers (58.3% vs. 76.3%), antiplatelet agents (70.8% vs. 88.5%) and statins (52.9% vs. 87.6%) [26].

The importance of ischemic heart disease as a component of T2MI prognosis was also recently emphasized by the development of new risk scores, such as the T2-risk score [45]. Higher T2-risk scores are associated with the occurrence of subsequent MI or all-cause death at 1 year, resulting in good performance in the derivation cohort (AUC: 0.77; 95%CI: 0.73–0.79), and both the single-center (AUC: 0.83 [95%CI: 0.77–0.88] and multicenter validation cohorts (AUC: 0.74 [95%CI: 0.64–0.83]) [45].

Finally, revascularization procedures were significantly less likely to be performed in patients with T2MI [26]. To date, although CAD in T2MI is common and associated with worse prognosis, no randomized controlled trials have evaluated invasive procedures and secondary prevention medications in this specific population, and there are no recommendations for a risk assessment or treatment strategy.

Table 3. Prognosis of T2MI patients with CAD.

First author (date)	Follow-up	T2MI patients (CAD/no CAD)	Endpoint	Death rate (T2MI CAD / T1MI CAD / T2MI without CAD)	Crude HR [95%CI] (T2MI CAD vs T2MI without CAD)	Crude HR [95%CI] (T2MI CAD vs T1MI)	Adjusted HR [95%CI] (T2MI CAD vs T1MI)
Putot (2019) (RICO)	In-hospital	254/619	All-cause death	15.0 / 6.6 /
Baron (2016) (SWEDEHEART)	1.9 years	695/621	All-cause death	1.72 [1.45-2.03]	0.76 [0.61-0.94*]
Chapman (2018)	4.9 years	325/467**	MACE***	..	1.71 [1.31-2.24]	1.56 [1.29-1.88]	..

T2MI: type 2 myocardial infarction. T1MI: type 1 myocardial infarction. CAD: coronary artery disease. RICO: Observatoire des Infarctus de la Côte d'Or. SWEDEHEART: Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. MACE: major adverse cardiovascular events

* adjustment for age, sex, comorbidities, treatments, triggering mechanisms, and troponin concentration

** T2MI or myocardial injury

*** defined as cardiovascular death or subsequent myocardial infarction

9. Conclusions

The underlying pathophysiology of T2MI is characterized by heterogeneous conditions leading to a mismatch between myocardial oxygen supply/demand, in association with older age and comorbidities. In addition to these underlying ischemic triggers, CAD is a frequent and severe condition in patients admitted for T2MI, in whom invasive strategies and secondary preventive medications are underused. Recent findings indicate that CAD has a strong, deleterious long-term predictive value in T2MI. Identifying underlying CAD may, thus, improve risk stratification in T2MI patients and provide a rationale for the future development of preventive therapies to reduce the risk of recurrent CV events. Machine learning models using multimodal data (patient information and ECG) have been suggested to improve MI detection [46], and integrative models, including medical data such as CAD, could thus potentially help to accurately classify T2MI and T1MI in the future.

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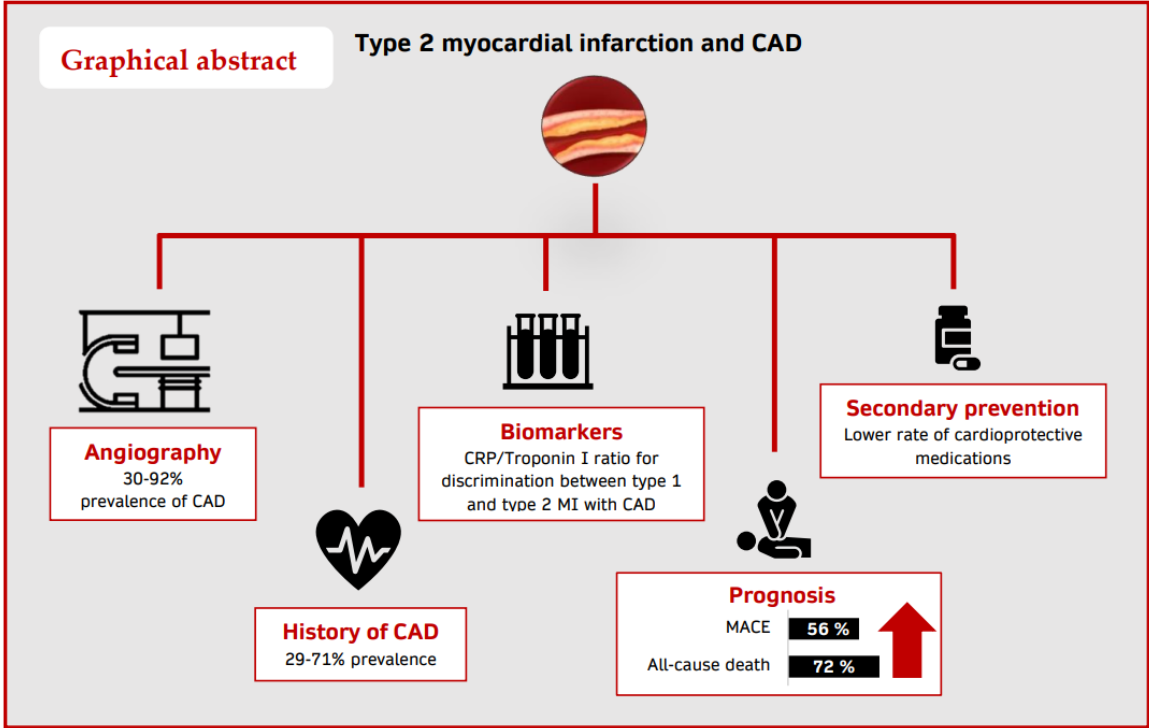
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CAD: coronary artery disease. MI: myocardial infarction. CRP : C-reactive protein. MACE : main adverse cardiac events.

4. Discussion générale

Depuis 2001, l'observatoire RICO représente une base de données unique en France avec un recueil prospectif, continu et exhaustif des paramètres cliniques, biologiques, coronarographiques, des données de la prise en charge et du suivi des patients présentant un IDM en Côte d'Or⁴⁹. La représentativité des données épidémiologiques issues du RICO a été validée par rapport aux données de référence du programme national French Registry on Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST-MI), dont le CHU de Dijon est l'un des principaux centres depuis 20 ans⁵⁷. Le registre monocentrique REACTIV, plus récent, représente l'homologue Sub-Saharien de l'observatoire RICO, dont il s'est inspiré en reprenant la même définition des variables, et est aujourd'hui l'un des registres les plus importants d'Afrique Sub-Saharienne⁴³.

Ce travail de thèse avait pour objectif de mieux caractériser l'épidémiologie et les facteurs pronostiques de l'IDM de type 2, à partir de ces deux bases de données régionales. L'IDM type 2 est une entité précisée il y a plus de 10 ans, à partir d'un concept physiopathologique particulièrement complexe et hétérogène dans sa traduction clinique. Nous avons cherché à évaluer la pertinence d'un ajustement de la classification des IDM, proposée en 2019 par de Lemos et al⁴⁷, pour individualiser des groupes plus homogènes dans leurs caractéristiques épidémiologiques et pronostiques, reposant notamment sur la présence ou non d'une maladie coronaire obstructive.

Apport d'une nouvelle classification des sous-types d'IDM

Une partie de notre travail a été menée en réalisant une reconsidération des cas d'IDM de type 1 et de type 2 selon la nouvelle classification proposée en 2019 ⁴⁷, sur plus de 4500 patients consécutifs du RICO, après l'adjudication systématique qui était réalisée selon les critères de la définition universelle de l'IDM en vigueur ⁹. La distinction entre IDM de type 1 et de type 2, et avec les *NIMI*, peut être difficile en pratique clinique, même si leur physiopathologie est différente. Des algorithmes d'aide au diagnostic différentiel sont disponibles, en présence d'un contexte clinique évocateur d'ischémie myocardique ^{9,30}. Ces modèles prennent en compte les critères ECG (IDM ST+ et IDM ST-), la présence ou non d'évidence clinique d'inadéquation apport / besoin en oxygène du myocarde, les données de la coronarographie (présence ou non d'une athéro-thrombose), et également de l'imagerie non invasive (échocardiographie, scanner cardiaque).

Les dernières recommandations de l'ESC indiquent qu'en l'absence de preuve concernant les stratégies de prise en charge dans l'IDM de type 2, notamment les traitements cardio-protecteurs, l'identification et la correction des conditions déclenchantes ischémiques restent pertinentes (transfusion sanguine, oxygénothérapie etc), accompagnées d'un contrôle strict des facteurs de risque CV ¹⁰. Cependant, une méta-analyse récente a mis en évidence le faible recours aux médicaments cardio-protecteurs chez les patients atteints d'IDM de type 2 (par rapport à l'IDM de type 1), en particulier les bêtabloquants (58,3 % contre 76,3 %), les antiplaquettaires (70,8 % contre 88,5 %) et les statines (52,9 % contre 87,6 %) ³².

Notre travail a permis, à partir de cette large base de population de patients hospitalisés enUSIC pour IDM, de montrer la pertinence de la proposition de re-classification de l'IDM. En effet, cette nouvelle classification distingue 2 phénotypes parmi les patients atteints d'IDM de type 2, avec un pronostic assez divergent. La présence d'une maladie coronaire obstructive parmi les patients atteints d'IDM de type 2 (type 2A) est associée à un pronostic péjoratif,

comparativement aux IDM de type 2B et même aux IDM de type 1A. Nos données issues de l'analyse du RICO retrouvent une surmortalité de 40% à 1 an pour la mortalité toutes causes pour ce type d'IDM (RR 1,362; 95%CI 1,029-1,802). Cependant, la mortalité CV reste plus élevée dans l'IDM de type 1A. De nouvelles perspectives thérapeutiques peuvent être considérées à partir de cette nouvelle classification, en particulier la place des traitements cardio-protecteurs dans l'IDM de type 2A. Cependant, comme évoqué précédemment, on ne dispose pas de données validées par des études interventionnelles sur cette approche thérapeutique en pratique clinique ¹⁰.

Par ailleurs, l'intérêt de cette classification en 2 groupes au sein des IDM type 2 réside aussi dans l'homogénéisation des caractéristiques cliniques. Dans l'IDM de type 2A, les patients sont plus âgés (d'environ 5 ans), et présentant davantage de facteurs de risque CV « traditionnels » (hypertension artérielle, hypercholestérolémie, diabète) et d'antécédents CV. Enfin, nos travaux ont permis de mettre en évidence des facteurs déclenchants préférentiels selon la présence ou l'absence de maladie coronaire. Ainsi, l'anémie et le syndrome de réponse inflammatoire systémique (SRIS) étaient les principaux facteurs retrouvés dans les IDM de type 2A, tandis que les tachyarythmies étaient davantage retrouvées dans les IDM de type 2B. Les autres mécanismes étaient globalement similaires dans les 2 groupes. Il est intéressant de noter que dans le registre *Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies* (SWEDEHEART), des mécanismes déclencheurs préférentiels ont été identifiés dans l'IDM de type 2, selon la présence ou l'absence d'une coronaropathie obstructive sous-jacente. La tachyarythmie et l'anémie aiguë et /ou un saignement étaient plus fréquents en présence d'une maladie coronaire obstructive, tandis que l'insuffisance respiratoire était plus souvent rencontrée en absence de maladie coronaire obstructive ³⁴. In fine, nos travaux soutiennent l'hypothèse que cette nouvelle

classification pourrait aider à évaluer des stratégies de prise en charge personnalisée des IDM de type 2.

Prévalence de la maladie coronaire chez les IDM type 2

Les données du RICO retrouvent une prévalence importante de la maladie coronaire parmi les patients présentant un IDM de type 2, qui est documentée dans plus des deux-tiers des cas (68,6%) en considérant des sténoses à la coronarographie d'au moins 50%. Ces données sont en accord avec les données de la littérature ^{33,34}. Dans le registre national suédois SWEDHEART, 57,6 % des patients avec IDM de type 2 présentaient une coronaropathie obstructive ³⁴. Dans l'étude *Catheter Sampled Blood Archive in Cardiovascular Diseases* (CASABLANCA), une coronarographie a été réalisée chez les 152 patients ayant présenté un IDM de type 2, dont la majorité (61,2 %) présentait une atteinte coronaire bitronculaire (sténose ≥ 50 %) ³³. Les critères angiographiques pour définir une maladie coronaire obstructive ne sont pas toujours uniformes (entre 50 et 70%), ceci pouvant être à l'origine d'une sous-estimation des coronaropathies obstructives dans l'IDM de type 2 dans certaines études ^{32,33}. Une coronaropathie obstructive n'est retrouvée que dans 34% des cas, dans la méta analyse de White et al ³², ayant inclus 40 études et près de 98 930 patients (dont 13 803 avec IDM de type 2) alors que la coronarographie n'a été réalisée que chez 34,1% des patients atteints d'IDM de type 2. Les différences observées dans les travaux sur la prévalence de la coronaropathie dans l'IDM de type 2 peuvent ainsi être en partie attribuées au taux souvent faible de réalisation de la coronarographie. Sur un échantillon représentatif de la population américaine en 2018, Smilowitz et al, ont reporté un taux encore plus faible de réalisation de la coronarographie, estimé à 11,2% ³¹. Malgré ce faible taux de réalisation de la coronarographie, une réduction de 30% de la mortalité est observée chez les patients bénéficiant d'une stratégie invasive (OR 0.70; 95% CI, 0.59-0.84) ³¹. A la différence de l'IDM de type 1, où la coronarographie constitue la

pièce angulaire du diagnostic, sa place reste discutée dans l'IDM de type 2. Une étude randomisée en cours, *the Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction* (ACT-2), vise à répondre à cette question, avec une analyse de la mortalité toutes causes et une analyse coût / efficacité avec ou sans coronarographie (ou coroscanner selon la préférence locale) à 2 ans ⁵⁸.

Valeur pronostique de la maladie coronaire chez les IDM type 2

Peu d'études ont rapporté la valeur pronostique à court ³⁹ et à long terme ^{34,38} de la présence d'une maladie coronaire significative parmi les patients atteints d'IDM de type 2. Parmi des patients atteints d'IDM présentant une maladie coronaire obstructive, la mortalité hospitalière toutes causes semble plus importante parmi les IDM de type 2 (15% vs. 7% pour les IDM de type 1, $p < 0,001$) tandis que la mortalité CV ne semble pas affectée ³⁹. Après un suivi de 5 ans, la présence d'une maladie coronaire significative est associée à la survenue plus importante d'événements CV majeurs, parmi les patients atteints d'IDM de type 2 ou de *NIMI* comparativement aux IDM de type 1 ³⁸. Ces résultats sont en faveur de la pertinence pronostique de la nouvelle classification de de Lemos, et soulignent l'importance d'identifier la maladie coronaire chez les patients atteints d'IDM de type 2 pour la stratification du risque. En phase avec nos travaux suggérant que le pronostic de l'IDM de type 2 est influencé par la présence d'une coronaropathie obstructive, un nouveau score pronostique dans l'IDM de type 2 vient d'être développé (*T2-risk score*) ⁵⁹, qui intègre la présence de la maladie coronaire en tant que variable. Spécifiquement développé pour les IDM de type 2 dans le cadre d'une étude multicentrique prospective sur une large base de population, il a montré son efficacité pour la stratification du risque d'évènement CV (IDM ou décès) à 1 an.

Nos travaux ont fait émerger la place de la maladie coronaire dans la stratification du risque des IDM type 2 en pratique clinique. C'est pourquoi nous nous sommes intéressés à une revue

générale de la littérature sur la maladie coronaire et l'IDM de type 2. La prévalence de la maladie coronaire à partir des données de la coronarographie est très variable, estimée entre 30 et 92% selon le taux de coronarographie (biais d'inclusion), mais aussi selon les seuils d'obstruction coronaire considérés (50% ou 70%). Dans l'étude CASABLANCA, parmi les patients atteints d'IDM de type 2, 47,7% avaient une sténose coronaire tandis que 61,2% présentaient une sténose $\geq 50\%$ ³³. Cette variabilité semble également influencée par le genre, puisque les femmes présentaient moins de maladie coronaire obstructive ⁶⁰, comme observé dans la maladie coronaire dans la littérature ⁶¹.

En l'absence des données d'imagerie coronaire, une autre façon d'appréhender la maladie coronaire dans l'IDM de type 2 est l'analyse des antécédents de maladie coronaire documentés à partir des dossiers médicaux ^{62,28,63}. Chez des patients admis aux urgences, un antécédent de maladie coronaire obstructive était un facteur prédictif indépendant de présenter un IDM de type 2 par rapport un IDM de type 1, en augmentant cette probabilité de 40% ³⁹. Enfin, une coronaropathie significative augmente le risque à la fois de présenter une récurrence d'IDM de type 1 (RR ajusté = 1,34 ; IC95% 1,28 - 1,42) et de type 2 (RR ajusté = 1,11 ; IC95% 1,07 - 1,16) au suivi à 1 an ⁶³.

La discrimination entre les IDM de type 1 et IDM de type 2 en présence d'une coronaropathie significative est difficile en pratique clinique, en l'absence de biomarqueurs spécifiques. Parmi les outils biologiques à disposition pour distinguer IDM de type 1 et IDM de type 2 en présence d'un antécédent de maladie coronaire, notre groupe a montré que le ratio C-Réactive Protéine (CRP) / TnIc a une meilleure valeur prédictive (Aire sous la courbe (AUC) = 0,84 ; IC95% 0,81 - 0,87) pour discriminer les 2 types d'IDM ³⁹, comparativement à la CRP et la TnIc isolément. D'autres équipes ont proposé le ratio N-terminal pro-brain natriuretic peptide (Nt pro-BNP) / TnIc ⁶⁴ ou une combinaison de trois paramètres (Nt pro BNP, TnIc et l'âge) ⁶⁵ pour aider à différencier les IDM de type 1 et de type 2. Ces deux études retrouvaient des valeurs prédictives

superposables (AUC = 0,76 ; IC95% 0,61-0,92 et AUC = 0,76 ; IC95% 0,67-0,84, respectivement), toutefois inférieures à celle du ratio CRP/TnIc mise en évidence par notre groupe.

Nous nous sommes ensuite intéressés à l'étude de l'IDM de type 2 dans une population d'Afrique sub-Saharienne. Nos résultats retrouvent une fréquence relativement faible (14%) de l'IDM de type 2, qui concerne des patients plus jeunes (54 ans) que ceux présentant un IDM de type 1 (58 ans), sans toutefois de différence d'âge significative. Ces données diffèrent largement de celles du RICO, où l'âge médian au diagnostic d'IDM de type 2 est de 77 ans, soit 10 ans de plus que pour l'IDM de type 1²⁸. De façon surprenante, les patients présentant un IDM de type 2 présentaient moins de facteurs de risque CV et de comorbidités que ceux présentant un IDM de type 1, à la différence là aussi de la plupart des données occidentales sur cette thématique spécifique³⁰, notamment celles du RICO²⁸. Ces données semblent remettre en cause le concept de « maladie gériatrique » attribuée aux IDM de type 2 comme présentation exclusive de la pathologie^{18,66}, et illustrent l'hétérogénéité épidémiologique de cette entité. Notre étude Ivoirienne retrouve également un profil différent en ce qui concerne les facteurs déclenchants des IDM de type 2. Les deux triggers principaux retrouvés sont l'embolie coronaire (24,2%) et les tachyarythmies (16,1%), en particulier la fibrillation atriale / flutter. Ces facteurs déclenchants sont différents de ceux retrouvés dans le RICO, où les infections aiguës (39%) en particulier respiratoires sont prépondérantes, suivies des tachyarythmies (10%)²⁸. Toutefois, certaines de ces différences peuvent être expliquées par les caractéristiques démographiques et sanitaires des populations. Contrairement aux pays occidentaux à la population vieillissante, la population Sub-Saharienne, et en particulier en Côte d'Ivoire, a une croissance démographique dynamique et une espérance de vie plus faible⁶⁷. En phase avec les caractéristiques démographiques, les patients atteints d'infarctus sont donc plus jeunes que dans les pays développés, avec une nette différence d'environ 10 ans⁴². Les patients ivoiriens inclus dans le

registre REACTIV avaient un âge moyen de 56 ans sur la période 2010-2016 (765 patients) ⁴³. Cette population d'IDM jeune se caractérise également par un faible taux de comorbidités et de facteurs de risque CV, qui toutefois augmentent graduellement avec l'âge. Néanmoins, ce résultat doit être interprété avec précaution compte tenu de la faible taille de notre population d'étude et d'autres études prospectives plus larges et multicentriques, avec une évaluation de l'exhaustivité des inclusions, sont nécessaires, afin de confirmer ces concepts.

Il est également intéressant de noter qu'il existerait des disparités ethniques vis à vis de l'IDM de type 2 ⁶⁸. Parmi les Afro-Américains, il a été reporté un taux plus élevé d'hospitalisations pour IDM de type 2 que pour IDM de type 1 (15,9% vs 11,6%), comparativement à la population blanche ou hispanique ⁶⁸. Compte tenu de la diversité ethnique caractérisant la population Ivoirienne, il pourra être intéressant de préciser davantage la prévalence dans les différentes ethnies. Ces données encore limitées soulignent l'intérêt particulier de développer cette thématique dans une population d'Afrique Sub-Saharienne.

5. Conclusion

L'IDM de type 2, habituellement considéré comme une pathologie gériatrique, du fait de l'âge avancé des patients et de la fréquence des comorbidités, semble en réalité présenter une grande hétérogénéité en fonction de la base de populations étudiée, de son profil démographique, ses facteurs de risque et de l'accès aux soins de santé, comme en atteste l'analyse parallèle des données des deux registres homologues RICO et REACTIV. Une population africaine jeune, à faible risque CV et sans coronaropathie sévère, représentait jusqu'à présent un profil non décrit par les études sur les populations des pays occidentaux mais qui semble pourtant concernée par ce type d'IDM.

D'autre part, nous montrons que la présence d'une maladie coronaire est un élément pronostique central de l'approche des IDM de type 2, tel que proposé par de Lemos et al et souligné par notre revue systématique. La distinction entre IDM de type 2 avec et sans maladie coronaire significative permet de créer des groupes de patients plus homogènes dans leurs caractéristiques épidémiologiques et pronostiques, préalable nécessaire à l'établissement de protocoles thérapeutiques spécifiques. La forte valeur pronostique de la maladie coronaire dans l'IDM de type 2 retrouvée dans nos travaux souligne l'importance de l'identification de cette condition spécifique.

6. Perspectives

Approche diagnostique

Comme nous l'avons évoqué, l'amélioration du diagnostic différentiel des différents types d'IDM représente un enjeu clinique majeur. L'imagerie, en particulier l'IRM myocardique, pour aider à la différenciation IDM de type 2 / lésions myocardiques non ischémiques ³⁵ représente une voie de recherche prometteuse. En effet, il a été montré que l'IRM myocardique pouvait être normale dans les IDM à coronaires indemnes de lésions obstructives, tel que démontré dans le registre suédois SWEDHEART ⁶⁹. La valeur ajoutée du scanner coronaire est en cours d'évaluation ^{36,37}, en particulier couplée à la réalisation de la Fractional Flow Reserve (FFR) pour l'identification des lésions coronaires pourvoyeuses d'ischémie dans l'IDM de type 2, car plusieurs facteurs causals peuvent être intriqués chez ces patients ³⁶. Dans une étude prospective récente ayant analysé 50 patients atteints d'IDM de type 2, 26% des participants présentaient des sténoses coronaires hémodynamiquement significatives, alors que 42% avaient des sténoses d'au moins 50% ³⁶. De plus, l'apport de l'intelligence artificielle devra être évalué pour améliorer le diagnostic différentiel, et des modèles de machine learning ont été proposés pour améliorer la détection de l'IDM ⁷⁰.

Approche pronostique

De plus, comme on l'a discuté précédemment, une approche pronostique personnalisée peut représenter une aide pertinente à la stratification du risque des IDM type 2. Dans ce cadre, nous nous proposons d'évaluer l'impact pronostique des principaux facteurs déclenchants identifiés dans notre étude, en fonction de la présence et de l'absence de maladie coronaire sous-jacente. Ainsi, l'anémie était plus fréquemment observée dans l'IDM de type 2A, à l'instar de la série de Baron et al ³⁴ et elle était également associée à un pronostic défavorable après IDM. Il serait

possible de dégager des phénotypes particuliers d'IDM de type 2, en tenant compte à la fois de la présence d'une coronaropathie significative et de déclencheurs ischémiques particuliers. En effet, il a été montré que le pronostic à long terme (jusqu'à 6 ans) des IDM de type 2 est également étroitement lié au type de trigger ⁷¹. Parmi ces facteurs, le pronostic le plus péjoratif semble porté par l'hypoxie, probablement témoin d'une affection sous-jacente grave, tandis que les causes rapidement réversibles (telles que les tachyarythmies) seraient associées à une meilleure survie. Une approche individualisée par les principaux facteurs précipitants de l'IDM de type 2 est probablement nécessaire à l'élaboration de stratégies thérapeutiques adaptées, comme par exemple pour l'IDM post-infectieux ²⁶ ou l'IDM secondaire à l'anémie ⁷². Nous avons suggéré que la stratification du risque de mortalité dans l'IDM de type 2 doit intégrer la présence de la coronaropathie sous-jacente, à l'image du T2-risk score ⁵⁵. Ce score pourra être évalué sur des cohortes plus importantes, et en particulier dans le RICO.

Approche thérapeutique

Nous avons montré qu'alors que la maladie coronaire était fréquente dans l'IDM de type 2 et est associée à un pronostic péjoratif, le recours aux traitements cardio-protecteurs était encore très limité ³², de même que la réalisation de procédures interventionnelles. Ces constats doivent questionner les freins au respect des recommandations en vigueur et ouvrir la voie à des études pharmaco-invasives interventionnelles qui nécessitent au préalable une homogénéisation des groupes de patients, facilitée par les apports de la nouvelle classification. Ces études devraient concerner en priorité l'effet des médicaments cardio-protecteurs, notamment les bêtabloquants, inhibiteurs de l'enzyme de conversion (IEC), antiagrégants plaquettaires, et les statines. Le bénéfice de l'angioplastie coronaire chez les patients présentant un IDM de type 2A, fait l'objet d'une étude randomisée en cours ⁵⁸.

Enfin, nos travaux ont permis de challenger le concept de maladie gériatrique attribué à l'IDM de type 2, en mettant en évidence des caractéristiques démographiques particulièrement jeunes dans une population d'Afrique Sub-Saharienne. Ainsi, la diversité de l'épidémiologie des patients atteints d'IDM de type 2, en partie tributaire de la zone géographique considérée, alimente davantage la difficulté pour comprendre cette entité clinique encore floue. Des études multicentriques en Afrique Sub-Saharienne sont donc nécessaires, afin de mieux caractériser ce groupe de patients jeunes, à la recherche de facteurs de risque spécifiques pouvant aboutir à terme à d'éventuelles stratégies préventives. La récente mise en place du réseau collaboratif *Dijon-Abidjan Myocardial Infarction (DAMIN)* entre les centres de recherche CV du CHU de Dijon et de l'Institut de Cardiologie d'Abidjan et qui vise à développer les axes collaboratifs à partir des registres RICO et REACTIV, semble donc particulièrement prometteuse.

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8. Annexes

Annexe 1 : 4ème définition universelle de l'infarctus du myocarde

Annexe 2 : de Lemos JA, Newby LK, Mills NL. A Proposal for Modest Revision of the Definition of Type 1 and Type 2 Myocardial Infarction. Circulation. 2019;140(22):1773-5.

Fourth universal definition of myocardial infarction (2018)

Kristian Thygesen* (Denmark), Joseph S. Alpert* (USA), Allan S. Jaffe (USA), Bernard R. Chaitman (USA), Jeroen J. Bax (The Netherlands), David A. Morrow (USA), Harvey D. White* (New Zealand): the Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction

Authors/Task Force Members/Chairpersons: Kristian Thygesen* (Denmark), Joseph S. Alpert* (USA), Allan S. Jaffe (USA), Bernard R. Chaitman (USA), Jeroen J. Bax (The Netherlands), David A. Morrow (USA), Harvey D. White* (New Zealand), Hans Mickley (Denmark), Filippo Crea (Italy), Frans Van de Werf (Belgium), Chiara Bucciarelli-Ducci (UK), Hugo A. Katus (Germany), Fausto J. Pinto (Portugal), Elliott M. Antman (USA), Christian W. Hamm (Germany), Raffaele De Caterina (Italy), James L. Januzzi Jr (USA), Fred S. Apple (USA), Maria Angeles Alonso Garcia (Spain), S. Richard Underwood (UK), John M. Canty Jr (USA), Alexander R. Lyon (UK), P. J. Devereaux (Canada), Jose Luis Zamorano (Spain), Bertil Lindahl (Sweden), William S. Weintraub (USA), L. Kristin Newby (USA), Renu Virmani (USA), Pascal Vranckx (Belgium), Don Cutlip (USA), Raymond J. Gibbons (USA), Sidney C. Smith (USA), Dan Atar (Norway), Russell V. Luepker (USA), Rose Marie Robertson (USA), Robert O. Bonow (USA), P. Gabriel Steg (France), Patrick T. O’Gara (USA), Keith A. A. Fox (UK)

* Corresponding authors. Kristian Thygesen, Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard, DK-8200 Aarhus N, Denmark. Tel: +45 78452262, Fax: +45 78452260, Email: kthygesen@oncable.dk; kristhyg@rm.dk. Joseph S. Alpert, Department of Medicine, University of Arizona College of Medicine, 1501 N. Campbell Ave., P.O. Box 245037, Tucson AZ 85724-5037, USA. Tel: +1 5206262763, Email: jalpert@email.arizona.edu. Harvey D. White, Green Lane Cardiovascular Service, Auckland City Hospital, Private Bag 92024, 1030 Auckland, New Zealand. Tel: +64 96309992, Fax: 00 64 9 6309915, Email: harveyw@adhb.govt.nz.

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Expert Consensus Document • Myocardial infarction • Type 1 MI • Type 2 MI • Type 3 MI • Type 4a MI • Type 4b MI • Type 4c MI • Type 5 MI • Cardiac troponin • High sensitivity cardiac troponin • Myocardial injury • Prior myocardial infarction • Silent myocardial infarction • Recurrent myocardial infarction • Re-infarction • Cardiac procedural myocardial injury • Takotsubo syndrome • Myocardial infarction with non-obstructive coronary arteries (MINOCA)

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Abbreviations and acronyms

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
ARC-2	Academic Research Consortium-2
AUC	Area under the curve
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
CKD	Chronic kidney disease
CK-MB	Creatine kinase MB isoform
CMR	Cardiac magnetic resonance
CTCA	Computed tomographic coronary angiography
cTn	Cardiac troponin

cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CT	Computed tomography
CV	Coefficient of variation
EF	Ejection fraction
ECG	Electrocardiogram or electrocardiographic
HF	Heart failure
hs-cTn	High-sensitivity cardiac troponin
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
ISFC	International Society and Federation of Cardiology
LAD	Left anterior descending artery
LBBB	Left bundle branch block;
LoD	Limit of detection
LGE	Late gadolinium enhancement
LGE-CMR	Late gadolinium enhancement cardiac magnetic resonance
LV	Left ventricular
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MONICA	MONItoring of trends and determinants in Cardiovascular disease
MPS	Myocardial perfusion scintigraphy
NHLBI	National Heart, Lung, and Blood Institute
NSTEMI	Non-ST-elevation myocardial infarction
PET	Positron emission tomography
PCI	Percutaneous coronary intervention
POC	Point of care
RBBB	Right bundle branch block
SPECT	Single photon emission computed tomography
STEMI	ST-elevation myocardial infarction
ST-T	ST-segment–T wave
TIMI	Thrombolysis in Myocardial Infarction
TTS	Takotsubo syndrome
UDMI	Universal Definition of Myocardial Infarction
URL	Upper reference limit
WHF	World Heart Federation
WHO	World Health Organization

1 What is new in the Universal Definition of Myocardial Infarction?

What's new in the universal definition of myocardial infarction?

New concepts

- Differentiation of myocardial infarction from myocardial injury.
- Highlighting peri-procedural myocardial injury after cardiac and non-cardiac procedures as discrete from myocardial infarction.
- Consideration of electrical remodelling (cardiac memory) in assessing repolarization abnormalities with tachyarrhythmia, pacing, and rate-related conduction disturbances.
- Use of cardiovascular magnetic resonance to define aetiology of myocardial injury.
- Use of computed tomographic coronary angiography in suspected myocardial infarction.

Updated concepts

- Type 1 myocardial infarction: Emphasis on the causal relationship of plaque disruption with coronary athero-thrombosis; *new Figure 3.*
- Type 2 myocardial infarction: Settings with oxygen demand and supply imbalance unrelated to acute coronary athero-thrombosis; *new Figures 4 and 5.*
- Type 2 myocardial infarction: Relevance of presence or absence of coronary artery disease to prognosis and therapy.
- Differentiation of myocardial injury from type 2 myocardial infarction; *new Figure 6.*
- Type 3 myocardial infarction: Clarify why type 3 myocardial infarction is a useful category to differentiate from sudden cardiac death.
- Types 4-5 myocardial infarction: Emphasis on distinction between procedure-related myocardial injury and procedure-related myocardial infarction.
- Cardiac troponin: Analytical issues for cardiac troponins; *new Figure 7.*
- Emphasis on the benefits of high-sensitivity cardiac troponin assays.
- Considerations relevant to the use of rapid rule-out and rule-in protocols for myocardial injury and myocardial infarction.
- Issues related to specific diagnostic change ('delta') criteria for the use of cardiac troponins to detect or exclude acute myocardial injury.
- Consideration of new non-rate-related right bundle branch block with specific repolarization patterns.
- ST-segment elevation in lead aVR with specific repolarization patterns, as a STEMI equivalent.
- ECG detection of myocardial ischaemia in patients with an implantable cardiac defibrillator or a pacemaker.
- Enhanced role of imaging including cardiac magnetic resonance imaging for the diagnosis of myocardial infarction; *new Figure 8.*

New sections

- Takotsubo syndrome.
- MINOCA.
- Chronic kidney disease.
- Atrial fibrillation.
- Regulatory perspective on myocardial infarction.
- Silent or unrecognized myocardial infarction.

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ECG = electrocardiogram; MINOCA = myocardial infarction with non-obstructive coronary arteries; STEMI = ST-elevation myocardial infarction.

2 Universal definitions of myocardial injury and myocardial infarction: summary

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI*.

Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for *type 4a MI* and > 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable ($\leq 20\%$ variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of $> 20\%$. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.

Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

3 Introduction

In the late 19th century, post-mortem examinations demonstrated a possible relationship between thrombotic occlusion of a coronary artery and myocardial infarction (MI).¹ However, it was not until the beginning of the 20th century that the first clinical descriptions appeared describing a connection between the formation of a thrombus in a coronary artery and its associated clinical features.^{2,3} Despite these landmark observations, considerable time elapsed before general clinical acceptance of this entity was achieved, in part due to one autopsy study that showed no thrombi in the coronary arteries of 31% of deceased patients with an MI.⁴ The clinical entity was referred to as coronary thrombosis, although use of the term 'MI' ultimately prevailed. Over the years, several different definitions of MI have been used, leading to controversy and confusion. Hence, a general and worldwide definition for MI was needed. This occurred for the first time in the 1950–70s, when working groups from the World Health Organization (WHO) established a primarily electrocardiographic (ECG)-based definition of MI intended for epidemiological use.⁵ The original description, with minor modifications, is still used in epidemiological surveys (Figure 1).^{6–8}

With the introduction of more sensitive cardiac biomarkers, the European Society of Cardiology (ESC) and the American College of

Cardiology (ACC) collaborated to redefine MI using a biochemical and clinical approach, and reported that myocardial injury detected by abnormal biomarkers in the setting of acute myocardial ischaemia should be labelled as MI.⁹ The principle was further refined by the Global MI Task Force, leading to the Universal Definition of Myocardial Infarction Consensus Document in 2007, introducing a novel MI classification system with five subcategories.¹⁰ This document, endorsed by the ESC, the ACC, the American Heart Association (AHA), and the World Heart Federation (WHF), was adopted by the WHO.¹¹ The development of even more sensitive assays for markers of myocardial injury made further revision of the document necessary, particularly for patients who undergo coronary procedures or cardiac surgery. As a result, the Joint ESC/ACC/AHA/WHF Task Force produced the Third Universal Definition of Myocardial Infarction Consensus Document in 2012.¹²

Studies have shown that myocardial injury, defined by an elevated cardiac troponin (cTn) value, is frequently encountered clinically and is associated with an adverse prognosis.^{13,14} Although myocardial injury is a prerequisite for the diagnosis of MI, it is also an entity in itself. To establish a diagnosis of MI, criteria in addition to abnormal biomarkers are required. Non-ischaemic myocardial injury may arise secondary to many cardiac conditions such as myocarditis, or may be associated with non-cardiac conditions such as renal failure.¹⁵ Therefore, for

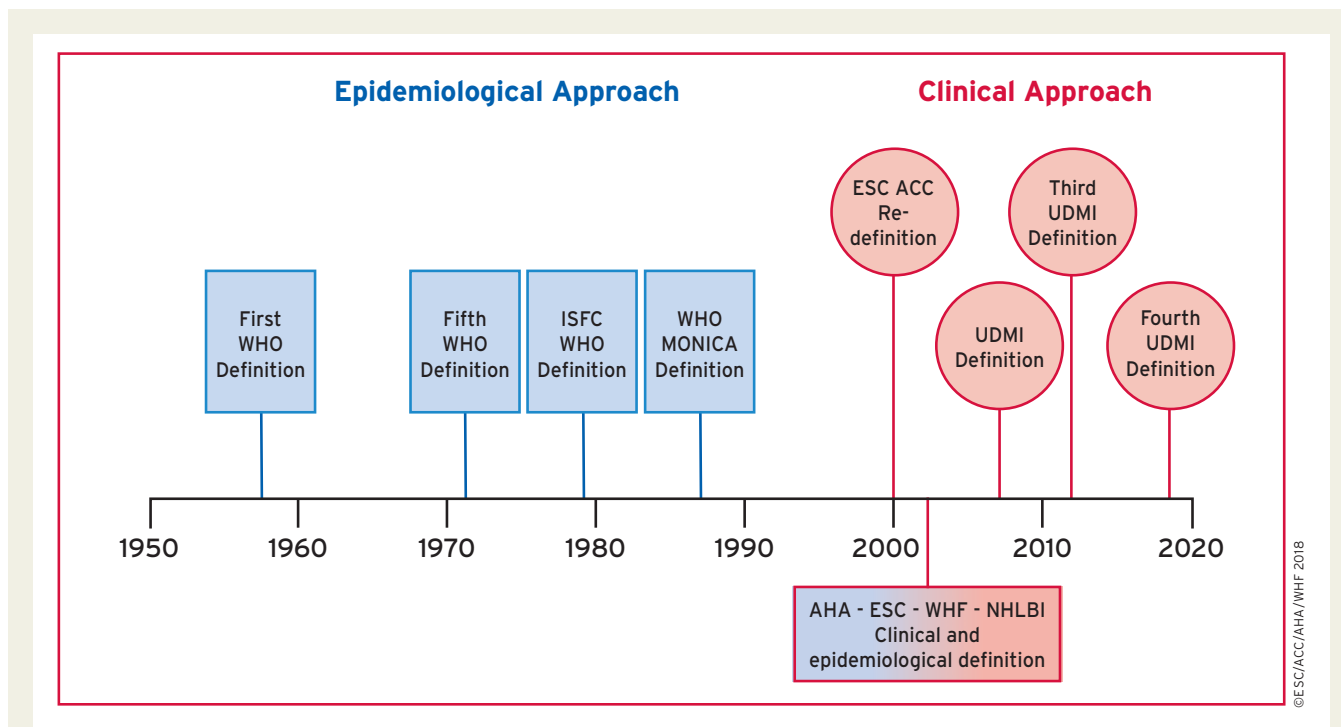


Figure 1 History of documents on the definition of myocardial infarction. ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; ISFC = International Society and Federation of Cardiology; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NHLBI = National Heart, Lung, and Blood Institute; UDMI = Universal Definition of Myocardial Infarction; WHF = World Heart Federation; WHO = World Health Organization.

patients with increased cTn values, clinicians must distinguish whether patients have suffered a non-ischaemic myocardial injury or one of the MI subtypes. If there is no evidence to support the presence of myocardial ischaemia, a diagnosis of myocardial injury should be made. This diagnosis can be changed if subsequent evaluation indicates criteria for MI. The current Fourth Universal Definition of Myocardial Infarction Consensus Document reflects these considerations through adhering to the clinical approach of the definition of MI.

Clinical criteria for MI

The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia.

4 Pathological characteristics of myocardial ischaemia and infarction

MI is defined pathologically as myocardial cell death due to prolonged ischaemia. Diminished cellular glycogen, and relaxed myofibrils and sarcolemmal disruption, are the first ultrastructural changes and are seen as early as 10–15 min after the onset of ischaemia.¹⁶ Mitochondrial abnormalities are observed as early as 10 min after coronary occlusion by electron microscopy and are progressive.¹⁷ It can take hours before myocyte necrosis can be identified by post-mortem examination in humans; this is in contrast to animal models, in which biochemical evidence of myocardial cell death due to apoptosis can be detected within 10 min of induced myocardial ischaemia in association with myocyte death.¹⁵ Experimentally, necrosis progresses from the subendocardium to the subepicardium over several hours. The time course may be prolonged by increased collateral flow, reduced determinants of myocardial oxygen consumption, and intermittent occlusion/reperfusion, which can precondition the heart.¹⁸ Timely implementation of reperfusion therapy, when appropriate, reduces ischaemic injury of the myocardium.^{19,20}

5 Biomarker detection of myocardial injury and infarction

Cardiac troponin I (cTnI) and T (cTnT) are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart.^{21,22} Increases in cTnI values have not been

reported to occur following injury to non-cardiac tissues. The situation is more complex for cTnT. Biochemical data indicate that injured skeletal muscle expresses proteins that are detected by the cTnT assay, leading to some situations where elevations of cTnT could emanate from skeletal muscle.^{23–27} Recent data suggest that the frequency of such elevations in the absence of ischaemic heart disease may be higher than originally thought.^{28,29} cTnI and cTnT are the preferred biomarkers for the evaluation of myocardial injury,^{12,21,22,30} and high-sensitivity (hs)-cTn assays are recommended for routine clinical use.²² Other biomarkers, e.g. creatine kinase MB isoform (CK-MB), are less sensitive and less specific.³¹ Myocardial injury is defined as being present when blood levels of cTn are increased above the 99th percentile upper reference limit (URL).^{12,21,22,30} The injury may be acute, as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL,

Criteria for myocardial injury

Detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.

or chronic, in the setting of persistently elevated cTn levels.

Although elevated cTn values reflect injury to myocardial cells, they do not indicate the underlying pathophysiological mechanisms, and can arise following preload-induced mechanical stretch or physiological stresses in otherwise normal hearts.^{32–34} Various causes have been suggested for the release of structural proteins from the myocardium, including normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, the formation and release of membranous blebs, and myocyte necrosis.^{27,35} Yet, it is not clinically possible to distinguish which increases of cTn levels are due to which mechanisms.³⁶ However, regardless of the mechanism, acute myocardial injury, when associated with a rising and/or falling pattern of cTn values with at least one value above the 99th percentile URL and caused by myocardial ischaemia, is designated as an acute MI.^{12,21,22,30} Histological evidence of myocardial injury with myocyte death can be detected in clinical conditions associated with non-ischaemic mechanisms of myocardial injury as well^{37,38} (Figure 2).

Myocardial ischaemic or non-ischaemic conditions associated with increased cTn values are presented in Table 1. The complexity of clinical circumstances may sometimes make it difficult to discriminate specific individual mechanism(s) of myocardial injury. In this situation, the multifactorial contributions resulting in myocardial injury should be described in the patient record.

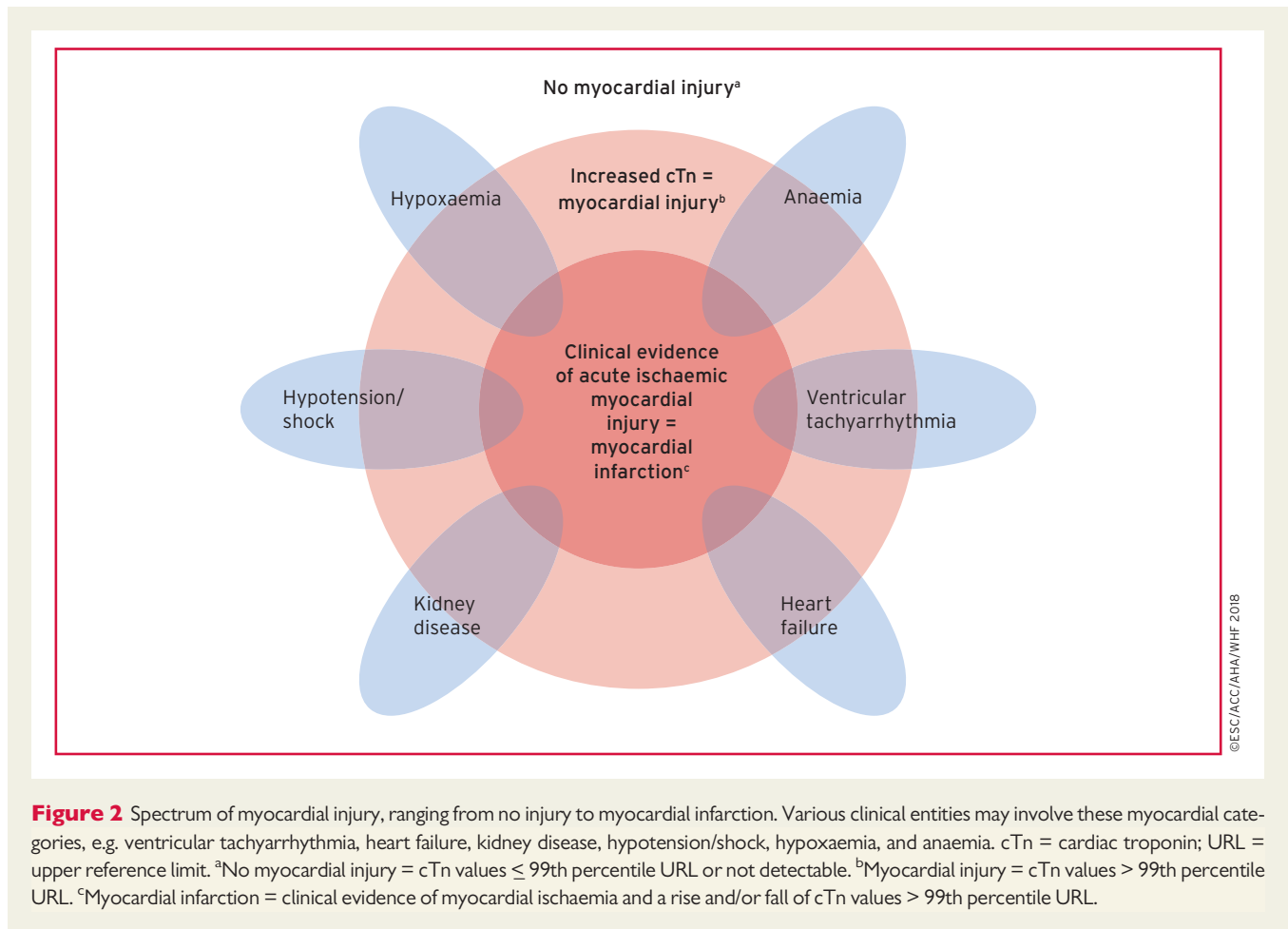


Table 1 Reasons for the elevation of cardiac troponin values because of myocardial injury

Myocardial injury related to acute myocardial ischaemia
Atherosclerotic plaque disruption with thrombosis.
Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance
<i>Reduced myocardial perfusion, e.g.</i> <ul style="list-style-type: none"> • Coronary artery spasm, microvascular dysfunction • Coronary embolism • Coronary artery dissection • Sustained bradyarrhythmia • Hypotension or shock • Respiratory failure • Severe anaemia
<i>Increased myocardial oxygen demand, e.g.</i> <ul style="list-style-type: none"> • Sustained tachyarrhythmia • Severe hypertension with or without left ventricular hypertrophy
Other causes of myocardial injury
<i>Cardiac conditions, e.g.</i> <ul style="list-style-type: none"> • Heart failure • Myocarditis • Cardiomyopathy (any type) • Takotsubo syndrome • Coronary revascularization procedure • Cardiac procedure other than revascularization • Catheter ablation • Defibrillator shocks • Cardiac contusion
<i>Systemic conditions, e.g.</i> <ul style="list-style-type: none"> • Sepsis, infectious disease • Chronic kidney disease • Stroke, subarachnoid haemorrhage • Pulmonary embolism, pulmonary hypertension • Infiltrative diseases, e.g. amyloidosis, sarcoidosis • Chemotherapeutic agents • Critically ill patients • Strenuous exercise

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For a more comprehensive listing, see^{39–41}

6 Clinical presentations of myocardial infarction

Onset of myocardial ischaemia is the initial step in the development of MI and results from an imbalance between oxygen supply and demand. Myocardial ischaemia in a clinical setting can most often be identified from the patient's history and from the ECG. Possible ischaemic symptoms include various combinations of chest, upper extremity, mandibular, or epigastric discomfort during exertion or at

rest, or an ischaemic equivalent such as dyspnoea or fatigue. Often, the discomfort is diffuse; not localized, nor positional, nor affected by movement of the region. However, these symptoms are not specific for myocardial ischaemia and can be observed in other conditions such as gastrointestinal, neurological, pulmonary, or musculoskeletal complaints. MI may occur with atypical symptoms such as palpitations or cardiac arrest, or even without symptoms.¹² Very brief episodes of ischaemia too short to cause necrosis can also cause cTn release and elevations. The involved myocytes can subsequently die due to apoptosis.⁴²

If myocardial ischaemia is present clinically or detected by ECG changes together with myocardial injury, manifested by a rising and/or falling pattern of cTn values, a diagnosis of acute MI is appropriate. If myocardial ischaemia is not present clinically, then elevated cTn levels may be indicative of acute myocardial injury if the pattern of values is rising and/or falling, or related to more chronic ongoing injury if the pattern is unchanging.¹⁴ Similar considerations are relevant when evaluating events that are potentially related to procedures that may cause myocardial injury and/or MI. Additional evaluations may lead to a need for the initial diagnosis to be revised.

Patients with suspected acute coronary syndrome (ACS) that are ruled out for MI with normal cardiac biomarker values (\leq 99th percentile URL) may have unstable angina or an alternative diagnosis. These patients should be evaluated and treated accordingly.^{11,43}

7 Clinical classification of myocardial infarction

For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate MI in patients with chest discomfort or other ischaemic symptoms, who develop new ST-segment elevations in two contiguous leads or new bundle branch blocks with ischaemic repolarization patterns as an ST-elevation MI (STEMI) (see section 27). In contrast, patients without ST-segment elevation at presentation are usually designated non-ST-elevation MI (NSTEMI). The categories of patients with STEMI, NSTEMI, or unstable angina are customarily included in the concept of ACS. In addition to these categories, MI may be classified into various types based on pathological, clinical, and prognostic differences, along with different treatment strategies.

7.1 Myocardial infarction type 1

MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as a type 1 MI. The relative burden of atherosclerosis and thrombosis in the culprit lesion varies greatly, and the dynamic thrombotic component may lead to distal coronary embolization resulting in myocyte necrosis.^{44,45} Plaque rupture may not only be complicated by intraluminal thrombosis but also by haemorrhage into the plaque through the disrupted surface (Figure 3).^{44,45}

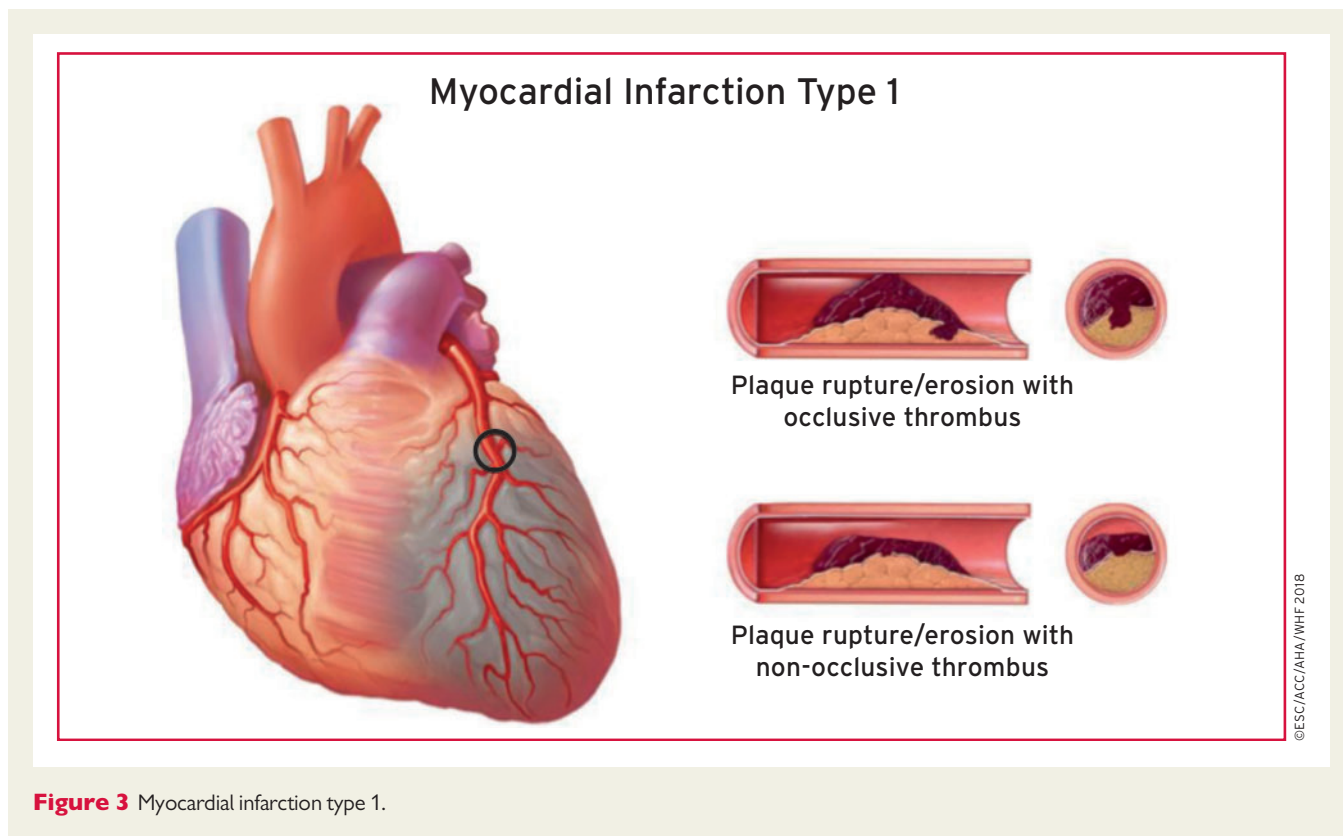


Figure 3 Myocardial infarction type 1.

Criteria for type 1 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.^a

cTn = cardiac troponin; ECG = electrocardiogram; URL = upper reference limit.

^aPost-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values.

It is essential to integrate the ECG findings with the aim of classifying type 1 MI into STEMI or NSTEMI in order to establish the appropriate treatment according to current Guidelines.^{46,47}

7.2 Myocardial infarction type 2

The pathophysiological mechanism leading to ischaemic myocardial injury in the context of a mismatch between oxygen supply and

demand has been classified as type 2 MI.^{10,12} By definition, acute atherothrombotic plaque disruption is not a feature of type 2 MI. In patients with stable known or presumed CAD, an acute stressor such as an acute gastrointestinal bleed with a precipitous drop in haemoglobin, or a sustained tachyarrhythmia with clinical manifestations of myocardial ischaemia, may result in myocardial injury and a type 2 MI. These effects are due to insufficient blood flow to the ischaemic myocardium to meet the increased myocardial oxygen demand of the stressor. Ischaemic thresholds may vary substantially in individual patients depending on the magnitude of the stressor, the presence of non-cardiac comorbidities, and the extent of underlying CAD and cardiac structural abnormalities.

Studies have shown variable occurrences of type 2 MI depending on criteria used for diagnosis. Some reports rely on specific predetermined oxygen mismatch criteria,^{48,49} whereas others apply more liberal criteria. Most studies show a higher frequency of type 2 MI in women. The short- and long-term mortality rates for patients with type 2 MI are generally higher than for type 1 MI patients in most but not all studies due to an increased prevalence of comorbid conditions.^{49–57} Coronary atherosclerosis is a common finding in type 2 MI patients selected for coronary angiography. In general, these patients have a worse prognosis than those without CAD.^{54–57} Prospective evaluations of the importance of CAD with type 2 MI using consistent definitions and approaches are needed.

It has been shown that the frequency of ST-segment elevation in type 2 MI varies from 3–24%.⁵³ In some cases, coronary embolism caused by thrombi, calcium or vegetation from the atria or ventricles, or acute aortic dissection may result in a type 2 MI. Spontaneous

coronary artery dissection with or without intramural haematoma is another non-atherosclerotic condition that may occur, especially in young women. It is defined as spontaneous dissection of the coronary artery wall with accumulation of blood within the false lumen, which can compress the true lumen to varying degrees (Figure 4).⁵⁸

All of the clinical information available should be considered in distinguishing type 1 MI from type 2 MI. The context and mechanisms of type 2 MI should be considered when establishing this diagnosis (Figure 5). The myocardial oxygen supply/demand imbalance attributable to acute myocardial ischaemia may be multifactorial, related either to: reduced myocardial perfusion due to fixed coronary atherosclerosis without plaque rupture, coronary artery spasm, coronary microvascular dysfunction (which includes endothelial dysfunction, smooth muscle cell dysfunction, and the dysregulation of sympathetic innervation), coronary embolism, coronary artery dissection with or without intramural haematoma, or other mechanisms that reduce oxygen supply such as severe bradyarrhythmia, respiratory failure with severe hypoxaemia, severe anaemia, and hypotension/shock; or to increased myocardial oxygen demand due to sustained tachyarrhythmia or severe hypertension with or without left ventricular

hypertrophy. In patients who undergo timely coronary angiography, description of a ruptured plaque with thrombus in the infarct-related artery may be helpful in making the distinction between type 2 MI vs. type 1 MI, but angiography is not always definitive, clinically indicated, or required to establish the diagnosis of type 2 MI.

Criteria for type 2 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary athero-thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

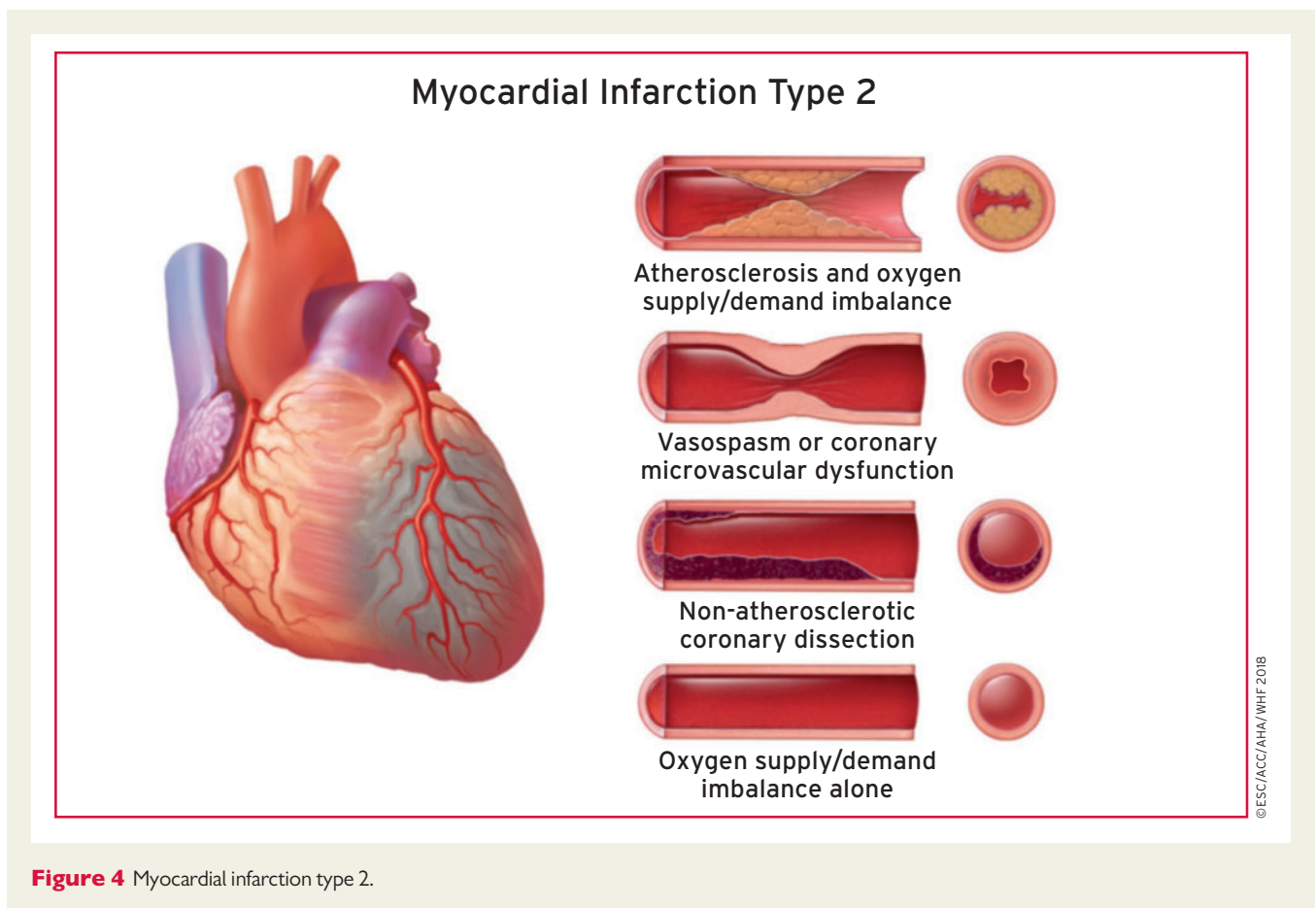


Figure 4 Myocardial infarction type 2.

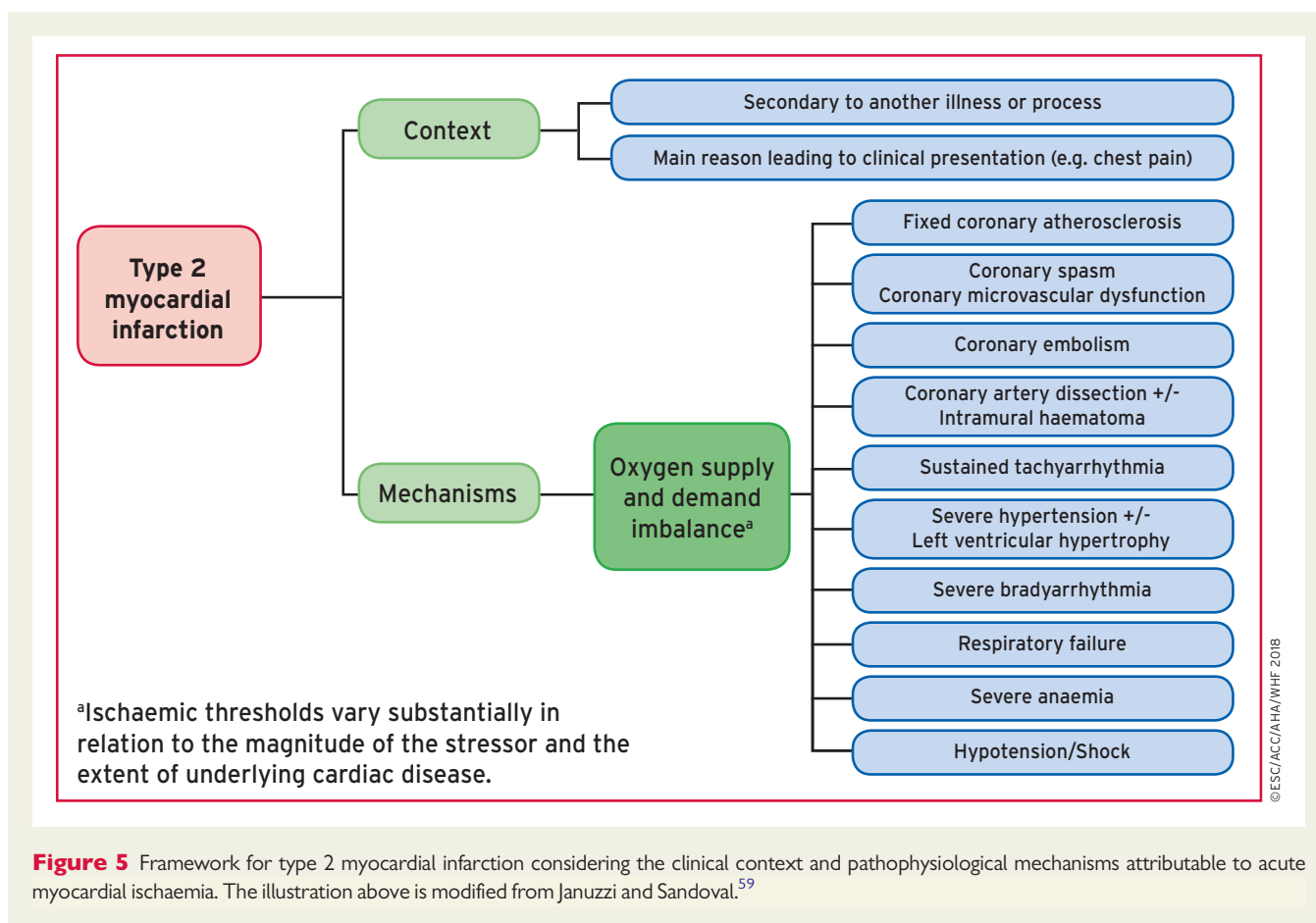


Figure 5 Framework for type 2 myocardial infarction considering the clinical context and pathophysiological mechanisms attributable to acute myocardial ischaemia. The illustration above is modified from Januzzi and Sandoval.⁵⁹

It appears advisable in the acute setting to treat the underlying ischaemic imbalance of oxygen supply and demand. This treatment may include volume adjustment, blood pressure management, administration of blood products, heart-rate control, and respiratory support.^{47,48} Depending on the clinical situation, coronary evaluations may be indicated to assess the likelihood of CAD. If it is present, the MI Guidelines may be applied in accordance with the ECG findings of STEMI or NSTEMI.^{46,47} However, if CAD is absent, the benefits of cardiovascular risk reduction strategies with type 2 MI remain uncertain.

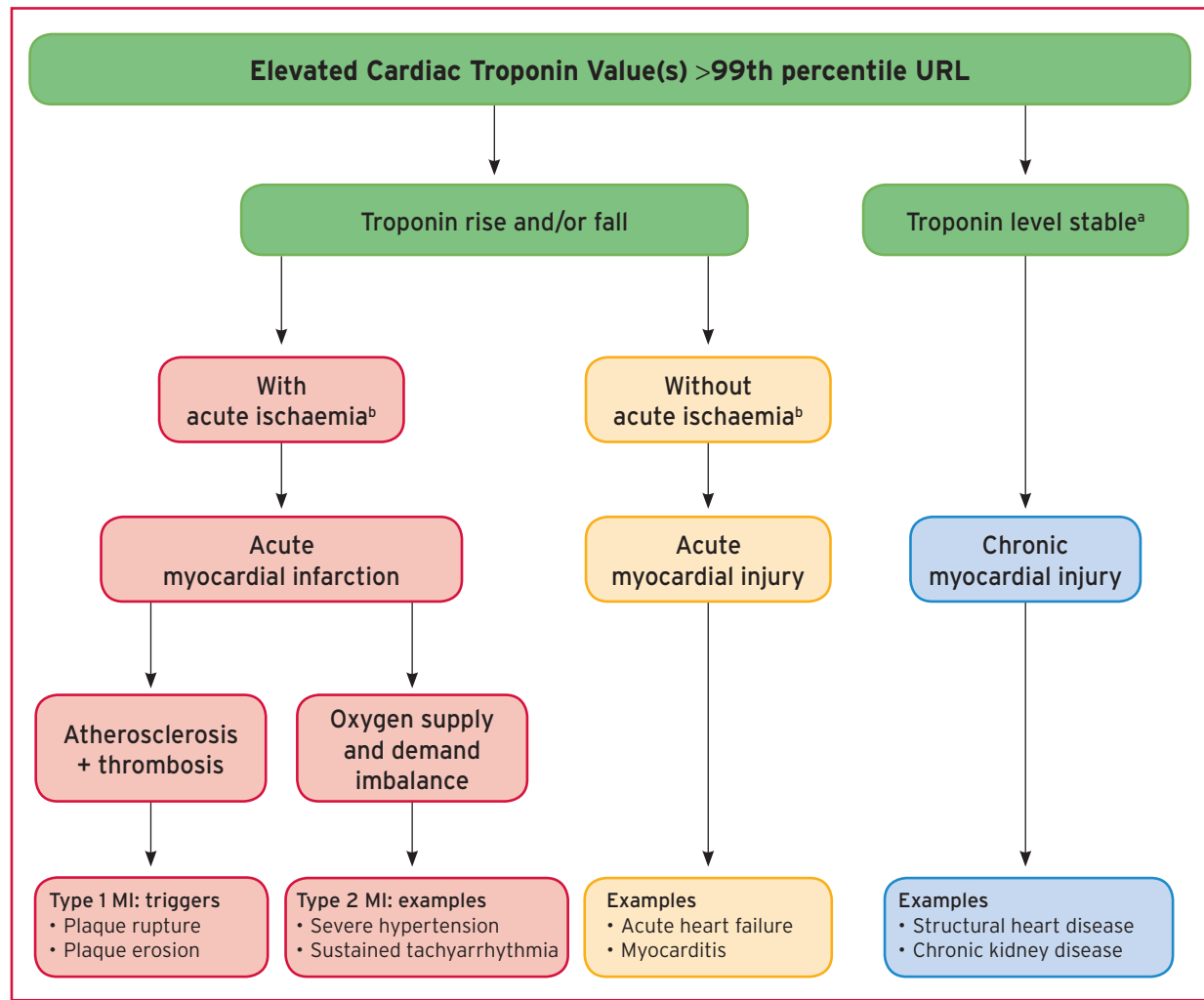
7.3 Myocardial infarction type 2 and myocardial injury

Type 2 MI and myocardial injury are frequently encountered in clinical practice and both are related to a poor outcome.^{13,14,49,51,56} A conceptual model to facilitate the clinical distinction between acute ischaemic myocardial injury with or without an acute atherothrombotic event (type 1 or type 2 MI) vs. conditions without acute ischaemic myocardial injury is displayed in *Figure 6*. Acute MI requires a rising and/or falling pattern of cTn values. Acute myocardial injury may also manifest such a pattern but if the injury is related to structural heart disease, the cTn values may be stable and unchanging.

Type 2 MI and non-ischaemic myocardial injury may coexist. It should be recognized that some disease entities may be on both sides of the diagram, e. g. acute heart failure that may occur in the context of acute myocardial ischaemia. Nevertheless, abnormal cTn values in the setting of acute and/or chronic heart failure are often better categorized as a myocardial injury condition. Few studies have compared the incidence and clinical features of type 2 MI vs. myocardial injury without acute myocardial ischaemia.

7.4 Myocardial infarction type 3

The detection of cardiac biomarkers in the blood is fundamental for establishing the diagnosis of MI.^{10,12} However, patients can manifest a typical presentation of myocardial ischaemia/infarction, including presumed new ischaemic ECG changes or ventricular fibrillation, and die before it is possible to obtain blood for cardiac biomarker determination; or the patient may succumb soon after the onset of symptoms before an elevation of biomarker values has occurred. Such patients are designated as having a type 3 MI, when suspicion for an acute myocardial ischaemic event is high, even when cardiac biomarker evidence of MI is lacking.^{10,12} This category allows the separation of fatal MI events from the much larger group of sudden death episodes that may be cardiac (non-ischaemic) or non-cardiac in origin. When a



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Figure 6 A model for interpreting myocardial injury. Ischaemic thresholds vary substantially in relation to the magnitude of the stressor and the extent of underlying cardiac disease. MI = myocardial infarction; URL = upper reference limit. ^aStable denotes $\leq 20\%$ variation of troponin values in the appropriate clinical context. ^bIschaemia denotes signs and/or symptoms of clinical myocardial ischaemia.

type 3 MI is diagnosed and a subsequent autopsy reveals recent evidence of an MI, with a fresh or recent thrombus in the infarct-related artery, the type 3 MI should be reclassified to a type 1 MI. Original investigations addressing the incidence of type 3 MI are sparse, but a study showed an annual incidence below 10/100 000 person-years and a frequency of 3–4% among all types of MI.⁶⁰

Criteria for type 3 MI

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

8 Coronary procedure-related myocardial injury

Cardiac procedural myocardial injury related to coronary revascularization procedures, whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), may be temporally related to the procedure itself, reflecting periprocedural issues, or may occur later reflecting complications of a device, such as early or late stent thrombosis or in-stent restenosis for PCI, or graft occlusion or stenosis with CABG. Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) allows assessment of procedural myocardial injury.^{61–63} When quantifying procedural injury using LGE-CMR before and shortly after PCI or CABG, it was found that 32% of patients had evidence of procedural myocardial injury.⁶³ Furthermore, it has been shown that patients with elevation of cTnI values after PCI

or after CABG have evidence of procedural myocardial injury on CMR imaging.^{61,62} For that reason, increased cTn values detected following a coronary revascularization procedure may reflect procedural myocardial injury. Of importance, if the baseline value before the procedure is above the 99th percentile URL, it is essential that cTn levels are stable prior to the evaluation in order to reliably establish the presence of acute procedural myocardial injury. It is not possible to determine, when intervening in a patient with an acute MI event resulting in an increased cTn level, how much of any given increase is related to the MI and how much is due to the procedure.

Criteria for cardiac procedural myocardial injury

Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (> 99th percentile URL) in patients with normal baseline values (\leq 99th percentile URL) or a rise of cTn values > 20% of the baseline value when it is above the 99th percentile URL but it is stable or falling.

A large proportion of patients have abnormal values of cTn after PCI, ranging from ~20–40% in stable CAD to 40–50% in MI.⁶⁴ The occurrence of procedural myocardial injury can be detected by the measurement of cTn before the procedure and repeated 3–6 h later. Where the second value is rising, further sampling should be performed to document the peak cTn value. Increasing levels after the procedure can only be attributed with certainty to procedural myocardial injury when the pre-procedural cTn values are normal (\leq 99th percentile URL), or if they are stable or falling. For patients that present with an ACS and undergo a prompt coronary revascularization procedure resulting in only a single pre-procedural baseline value that is normal or mildly elevated, followed by subsequent post-procedural values that continue to increase, the post-procedural increase should be attributed to the index event. Recent data corroborate the importance of elevated pre-procedure cTn values as a prognostic marker in patients that have values that rise after the procedure.⁶⁵ To diagnose procedural myocardial injury in the clinical setting of only a single pre-procedural cTn value, the cardiac Tn values would need to be stable or falling post-procedure, followed by a subsequent increase that exceeds the 99th percentile URL, and if the value has not returned to baseline, the increase should be > 20% with an absolute value > the 99th percentile URL.

9 Myocardial infarction associated with percutaneous coronary intervention (type 4a myocardial infarction)

Stand-alone post-procedural increases of cTn values are sufficient to establish a diagnosis of procedural myocardial injury but not for the diagnosis of type 4a MI. Type 4a MI requires an elevation of cTn values greater than five times the 99th percentile URL in patients with

normal baseline values or, in patients with elevated pre-procedure cTn in whom the cTn levels are stable (\leq 20% variation) or falling, the post-procedure cTn must rise > 20% to an absolute value more than five times the 99th percentile URL. In addition, there should be evidence of new myocardial ischaemia, either from ECG changes, imaging evidence, or from procedure-related complications associated with reduced coronary blood flow such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, slow flow or no-reflow, or distal embolization. The use of hs-cTn assays to diagnose type 4a MI (and type 5 MI) is an area of active research. Many hs-cTn assays are available, which have wide dynamic ranges. Different criteria may be required for different assays. However, it has recently been shown that the optimal hs-cTnT thresholds to predict cardiovascular events at 30 days and 1 year were very close to the five-fold increase suggested by the Third Universal Definition of Myocardial infarction.^{12,66,67} These criteria are therefore retained because of a lack of new scientific evidence that identifies superior criteria for defining this MI subtype. Other criteria that meet the definition of type 4a MI, regardless of hs-cTn or cTn values, are the development of new pathological Q waves or autopsy evidence of recent procedure-related thrombus in the culprit artery.

Criteria for PCI-related MI \leq 48 h after the index procedure (type 4a MI)

Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (\leq 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;^a
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.^b

^aIsolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but less than five times the 99th percentile URL.

^bPost-mortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria.

10 Stent/scaffold thrombosis associated with percutaneous coronary intervention (type 4b myocardial infarction)

A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI. It is important to indicate the time of the occurrence of the stent/scaffold thrombosis in relation to the timing of the PCI procedure. The following temporal categories are suggested: acute, 0–24 h; subacute, > 24 h to 30 days; late, > 30 days to 1 year; and very late > 1 year after stent/scaffold implantation.⁶⁸

11 Restenosis associated with percutaneous coronary intervention (type 4c myocardial infarction)

Occasionally MI occurs and—at angiography, in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory—is the only angiographic explanation since no other culprit lesion or thrombus can be identified. This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.

12 Myocardial infarction associated with coronary artery bypass grafting (type 5 myocardial infarction)

Numerous factors can lead to procedural myocardial injury during a CABG procedure. Many of them are related to the details of the cardiac preservation, the extent of the direct traumatic injury to the myocardium, as well as any potential ischaemic injury. For that reason, increases in cTn values should be expected after all CABG procedures,^{69,70} which need to be taken into account when comparing the extent of procedural myocardial injury after cardiac surgery with that associated with less invasive approaches. Depending on whether it is off-pump or on-pump surgery, procedural myocardial injury is observed among 32–44% of CABG patients when quantified by LGE-CMR.^{61,63} The area under the curve (AUC) and routine cTn sampling has demonstrated an excellent linear relationship with the mass of the new injury as defined by LGE-CMR. AUC for CK-MB is also good, although clearly inferior to cTnI.⁶⁹ However, these relationships vary depending on the nature of the procedure, the nature of the cardioplegia, and the specific assay used to measure cTn. Very high cTn values are most often associated with coronary artery-related events.^{61,63,69} Thus, although cardiac biomarkers and

especially cTn appear robust for the detection of procedural myocardial injury and also, in the presence of new myocardial ischaemia, for the detection of type 5 MI, a specific cut-off value for all procedures and all cTn assays is difficult to define. However, in order to ensure consistency with the analogous standards of the preceding definition of type 5 MI¹² and because of the lack of new scientific evidence that identifies superior criteria for defining this MI subtype, it is suggested that a cTn value > 10 times the 99th percentile URL is applied as the cut-off point during the first 48 h following CABG, occurring from a normal baseline cTn value (\leq 99th percentile URL), for diagnosing type 5 MI. It is important that the post-procedural elevation of cTn values is accompanied by ECG, angiographic, or imaging evidence of new myocardial ischaemia/new loss of myocardial viability.⁷¹ The higher cut-off of MI after CABG than after PCI (10 times vs. 5 times the 99th percentile URL) has been arbitrarily selected due to the occurrence of more unavoidable myocardial injury during surgery than during PCI.

It should be recognized that ST-segment deviation and T wave changes are common after CABG due to epicardial injury, and are not reliable indicators of myocardial ischaemia in this setting. However, ST-segment elevation with reciprocal ST-segment depression or other specific ECG patterns may be a more reliable finding of a potential ischaemic event.

Criteria for CABG-related MI \leq 48 h after the index procedure (type 5 MI)

CABG-related MI is arbitrarily defined as elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (\leq 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value still must be > 10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves;^a
- Angiographic documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

^aIsolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.

Marked isolated elevation of cTn values within the 48 h post-operative period, even in the absence of ECG/angiographic or other imaging evidence of MI, indicates prognostically significant cardiac procedural myocardial injury.⁷² The presence of significant procedural myocardial injury in patients with operative problems (e.g. difficulty coming off bypass, technically difficult anastomoses in a heavily calcified aorta, of perioperative evidence of myocardial ischaemia, etc.) should prompt clinical review of the procedure and/or consideration of additional diagnostic testing for possible type 5 MI.

13 Other definitions of myocardial infarction related to percutaneous coronary intervention or coronary artery bypass grafting

There is no universal consensus on the cTn or hs-cTn cut-off points that clearly distinguish cardiac procedural myocardial injury from MI. The distinction is made on the basis of an injury created by a flow-limiting complication during the procedure that results in sufficient myocardial ischaemia to generate a procedure-related MI. The size of the insult will determine the magnitude of the cTn release. Various groups have used multiples of the 99th percentile URL and set thresholds to diagnose periprocedural MIs for clinical trials.^{68,73}

Unless a standard assay is used for all analyses, given the heterogeneity of cTn assays, this approach could lead to very different values depending on the assay used locally. The Academic Research Consortium-2 (ARC-2) suggests a post-procedural cTn value ≥ 35 times the 99th percentile URL for both PCI and CABG in patients that have a normal baseline cTn value or in patients with elevated pre-procedure cTn values in whom the cTn levels are stable or falling. ARC-2 proposes that one ancillary criterion be required in addition to the ≥ 35 cTn rise to fulfill the definition of periprocedural MI. The ancillary criteria are one or more of the following: new significant Q waves (or equivalent), flow-limiting angiographic complications in a major epicardial vessel or > 1.5 mm diameter branch, or a substantial new loss of viable myocardium on echocardiography related to the procedure.⁶⁸ Furthermore, ARC-2 has defined stand-alone criteria for significant procedural myocardial injury if the rise in cTn is ≥ 70 times the 99th percentile URL (where the baseline is lower than the URL, elevated and stable, or falling).⁶⁸

14 Recurrent myocardial infarction

Incident MI is defined as the individual's first MI. When features of MI occur in the first 28 days after an incident event, the second event is not counted as a new MI for epidemiological purposes. If characteristics of MI occur after 28 days following an incident MI, it is considered to be a recurrent MI.¹¹

15 Re-infarction

The term re-infarction is used clinically for an acute MI that occurs within 28 days of an incident or recurrent MI.¹¹ The ECG diagnosis of suspected re-infarction following the initial MI may be confounded by the initial evolutionary ECG changes. Re-infarction should be considered when ST-elevation ≥ 1 mm recurs or new pathognomonic Q waves appear in at least two contiguous leads, particularly when associated with ischaemic symptoms. However, re-elevation of the ST-segment can also be seen in threatened myocardial rupture or in cases of pericarditis, and should lead to additional diagnostic evaluation.

In patients where re-infarction is suspected from clinical signs or symptoms following the initial MI, an immediate measurement of cTn

is recommended. A second sample should be obtained 3–6 h later or earlier with more sensitive cTn assays. If the cTn concentration is elevated, but stable or decreasing at the time of suspected re-infarction, the diagnosis of re-infarction requires a $> 20\%$ increase of the cTn value in the second sample.⁷⁴ If the initial cTn concentration is normal, the criteria for new acute MI apply.¹²

16 Myocardial injury and infarction associated with cardiac procedures other than revascularization

Cardiac procedures such as transcatheter valve interventions may cause myocardial injury, both by direct trauma to the myocardium and by creating regional ischaemia secondary to coronary obstruction or embolization. Ablation of arrhythmias involves controlled procedural myocardial injury by application of warming or cooling of the tissue. The extent of procedural myocardial injury can be assessed by serial cTn measurements. Increases of cTn values in this context should be considered as a procedural myocardial injury and not labelled as an MI unless the biomarker criteria and one of the ancillary criteria for acute myocardial ischaemia listed for type 5 MI are present.^{75,76}

17 Myocardial injury and infarction associated with non-cardiac procedures

Perioperative MI is one of the most important complications in major non-cardiac surgery and it is associated with a poor prognosis.^{77,78} Most patients who have a perioperative MI will not experience ischaemic symptoms due to anaesthesia, sedation, or pain relieving medications. Nevertheless, asymptomatic perioperative MI is as strongly associated with 30 day mortality as symptomatic MI.^{77,78} Knowledge about hs-cTn values at baseline can help to identify patients having chronic cTn elevation before surgery, as well as those at increased risk during and after the procedure.^{79,80} Measurement of hs-cTn in post-operative samples reveals that as many as 35% of patients have levels above the 99th percentile URL, and 17% have an elevation and a rising pattern of values indicative of evolving myocardial injury.⁸¹ Those with a rising pattern of elevated hs-cTn values are at particular risk; the greater the rise, the greater the risk.^{82,83}

The pathophysiological mechanism of perioperative MI is subject to debate. It is recognized that the perioperative period is characterized by increased cardiac metabolic demand that may lead to MI in patients with otherwise stable CAD.^{84,85} Thus, an angiographic investigation has identified demand myocardial ischaemia as the predominant aetiology of perioperative MI,^{84,85} which together with a rise and/or fall of cTn values indicates type 2 MI. However, other angiographic studies have detected coronary plaque rupture in ~ 50 – 60% of patients with perioperative MI,^{86,87} which qualifies as type 1 MI. On the other hand, perioperative myocardial injury without ancillary ischaemic evidence indicative of MI is a common complication after

non-cardiac surgery that is associated with substantial short- and long-term mortality on a level with perioperative MI.⁸³

Post-operative cTn surveillance is recommended for high-risk individuals. In order to properly interpret the aetiology of elevated post-operative values, a baseline pre-operative value is necessary to determine whether the increase is acute or more chronic. However, a diagnosis of MI still requires, in addition to an increase of cTn values, evidence of myocardial ischaemia that may be evident from the peri- and post-operative period, e.g. ST-segment changes on telemetry/ECG, repeated episodes of hypoxia, hypotension, tachycardia, or imaging evidence of MI. In the absence of evidence for acute myocardial ischaemia, a diagnosis of acute myocardial injury is more appropriate. Ongoing research suggests the possibility that interventions may be helpful in this clinical situation.

18 Myocardial injury or infarction associated with heart failure

Depending on the assay used, detectable to clearly elevated cTn values being indicative of myocardial injury may be seen in patients with heart failure (HF), both with reduced ejection fraction (EF) and with preserved EF.⁸⁸ Using hs-cTn assays, measurable hs-cTn concentrations may be present in nearly all patients with HF, with a significant percentage exceeding the 99th percentile URL, particularly in those patients with more severe HF syndromes, such as in acutely decompensated HF.⁸⁷

Beyond type 1 MI, multiple mechanisms have been proposed to explain measurable to pathologically elevated cTn concentrations in patients with HF.^{88,89} For example, type 2 MI may result from increased transmural pressure, small-vessel coronary obstruction, endothelial dysfunction, anaemia, or hypotension. Besides type 1 MI or type 2 MI, cardiomyocyte apoptosis and autophagy due to wall stretch have been experimentally demonstrated. Direct cellular toxicity related to inflammation, circulating neurohormones, and infiltrative processes may present with HF and abnormal cTn measurements indicating myocardial injury. Finally, exocytosis of the early releasable cytosolic troponin pool into the blood stream from stressed cardiomyocytes has also been suggested as a cause of elevated cTn values.⁸⁹

In the context of an acutely decompensated HF presentation, cTn should always be promptly measured and the ECG recorded, with the goal of identifying or excluding myocardial ischaemia as the precipitant. In this setting, elevated cTn values should be interpreted with a high level of suspicion for type 1 MI if a significant rise and/or fall of the marker is seen, especially if it is accompanied by chest discomfort or other symptoms suggestive of myocardial ischaemia, and/or if new ischaemic ECG changes or loss of myocardial function on non-invasive testing are found. Shortness of breath, the cardinal symptom of acutely decompensated HF, may be an ischaemic equivalent, but in the absence of corroborating evidence for a coronary mechanism, caution is advised in its interpretation. Coronary artery anatomy may be known and this knowledge may be used to interpret abnormal cTn results. However, further information—such as renal function, myocardial perfusion studies, coronary angiography, or

CMR—is often required to better understand the cause of deviant cTn values.

19 Takotsubo syndrome

Takotsubo syndrome (TTS) can mimic MI and is found in ~1–2% of patients presenting with suspected STEMI.⁹⁰ The onset of TTS is often triggered by intense emotional or physical stresses, such as bereavement. Over 90% of patients are post-menopausal women. Cardiovascular complications occur in ~50% of patients presenting with TTS, and the inpatient mortality is similar to STEMI (4–5%) due to cardiogenic shock, ventricular rupture, or malignant arrhythmias.⁹⁰ TTS usually presents similar to ACS. ST-segment elevation is frequent (44%), but the extent of the ST-segment elevation is usually widespread across the lateral and precordial leads, beyond that of a single coronary artery distribution. ST-segment depression occurs in < 10% of patients and after 12–24 h, deep, symmetric T wave inversion and QTc prolongation are typically observed.^{91,92}

There are usually transient elevations in cTn levels (> 95% of cases), but the peak cTn values observed are modest, and contrast with the large territory of ECG changes or left ventricular (LV) dysfunction. The rise and fall in cTn levels support an acute myocardial injury, secondary to the high catecholamine surges that are known to trigger cTn release from cardiomyocytes. Coronary vasospasm, high myocardial strain hypercontractility, or high ventricular afterload may also contribute to myocardial ischaemia. The diagnosis of TTS should be suspected when the clinical manifestations and ECG abnormalities are out of proportion to the degree of elevation of cTn values, and when the distribution of the LV wall motion abnormalities does not correlate with a single coronary artery distribution. However, coronary angiography and ventriculography are often needed to secure the diagnosis.

In most cases, the coronary arteries are angiographically normal, and where CAD is present (~15% cases) it is not sufficient to explain the observed pattern of regional wall motion abnormalities. Left ventriculography during catheterization and/or echocardiography may show a variety of LV regional wall motion abnormalities including apical (82% of patients), mid-ventricular (14.6%), basal (2.2%), or focal (1.5%) akinesis or hypokinesis in a circumferential pattern involving more than one coronary artery territory. Evidence of myocardial oedema is often seen on CMR imaging during the acute phase but LGE is usually absent. The recovery time for LV function varies from hours to several weeks.⁹³ Cardiac function may not return to normal, with persisting abnormalities of diastolic function, myocardial reserve during exercise, or rhythm disturbances at long-term follow-up in 10–15% of patients. In the absence of recovery of regional wall motion abnormalities, LGE-CMR is recommended to exclude MI with spontaneous recanalization.

The distinction between MI and TTS can be challenging, particularly when concurrent CAD is present (15% in the International Takotsubo Registry).⁹¹ Two additional features that are helpful in distinguishing TTS from acute MI are QTc prolongation > 500 ms during the acute phase and the recovery of LV function over 2–4 weeks. There are rare cases described where MI and TTS

coexist, e.g. MI-induced TTS or TTS with secondary plaque rupture, but this occurs where the acute regional wall motion abnormalities are more extensive than the culprit coronary artery territory, and fulfil the pattern and definition of TTS.⁹⁴

20 Myocardial infarction with non-obstructive coronary arteries

It is increasingly recognized that there is a group of MI patients with no angiographic obstructive CAD ($\geq 50\%$ diameter stenosis in a major epicardial vessel), and the term myocardial infarction with non-obstructive coronary arteries (MINOCA) has been coined for this entity.^{95,96} The diagnosis of MINOCA, like the diagnosis of MI, indicates that there is an ischaemic mechanism responsible for the myocyte injury (i.e. non-ischaemic causes such as myocarditis have been excluded). Furthermore, the diagnosis of MINOCA necessitates that obstructive CAD has not been inadvertently overlooked (e.g. spontaneous coronary artery dissection). The prevalence of MINOCA is estimated to be 6–8% among patients diagnosed with MI and more common in women than men, as well as in patients presenting with NSTEMI compared with those presenting with STEMI.^{96–98} Atherosclerotic plaque disruption and coronary thrombosis may be a cause of MINOCA, i.e. type 1 MI. However, coronary spasm and spontaneous coronary dissection may be involved as well, i.e. type 2 MI, along with other possible causes. Additional coronary imaging and functional testing methods may be useful to elucidate the mechanisms of ischaemia in MINOCA.⁴⁶

21 Myocardial injury and/or infarction associated with kidney disease

Many patients with chronic kidney disease (CKD) have elevation of cTn values.^{99,100} With hs-cTn assays, the majority of patients with end-stage renal disease will have elevation of hs-cTn values above the 99th percentile URL.^{99,101} This is particularly the case for hs-cTnT, which is more often elevated compared with hs-cTnI.^{99,102} It has been shown using hs-cTn assays that renal dysfunction is commonly associated with cardiovascular abnormalities.^{102–104} In autopsy studies, elevation of cTn values was invariably associated with evidence of myocardial injury.¹⁵ Recently, a minor effect on renal clearance of cTn has been shown when levels are low, but not in response to acute episodes of myocardial injury.¹⁰⁵ The mechanisms include increased ventricular pressure, small-vessel coronary obstruction, anaemia, hypotension, and possibly direct toxic effects on the myocardium associated with the uraemic state.⁸⁹ Cardiomyocyte apoptosis and autophagy due to acute wall stretch have been demonstrated experimentally.¹⁸ Thus, baseline elevation of cTn values is common, and because they reflect myocardial injury, such elevation is highly prognostic over time.⁹⁹

Diagnosing MI in patients with CKD and elevated cTn levels may be difficult if symptoms or ECG changes indicating myocardial ischaemia are absent. However, studies suggest that serial changes in cTn levels are equally effective in diagnosing MI in patients with CKD and in those with normal renal function.¹⁰⁶ If the level of elevated cTn values is unchanging, and the timing of the event makes a rising and/or falling pattern unlikely, the elevated level, even if substantial, is likely a reflection of chronic myocardial injury. This does not imply that these patients are free of CAD, since renal dysfunction and CAD are correlated. However, if a rising and/or falling pattern is present then the aetiology of the abnormal cTn values could be acute volume overload, congestive HF, or MI. If a rising and falling pattern is seen, and it is accompanied by ischaemic symptoms, new ischaemic ECG changes, or loss of viable myocardium on imaging, a diagnosis of acute MI is likely. There are no data to suggest that different criteria for the cTn decision levels are needed for these patients. At times, additional imaging studies may be necessary to determine the appropriate diagnosis. It should be noted that if CKD patients present late after the onset of chest pain, it may be difficult to observe a rise and/or fall of cTn values in the short-term, particularly when the baseline value is elevated. Such a situation should not obviate the diagnosis of MI when the clinical evidence is strong.

22 Myocardial injury and/or infarction in critically ill patients

Elevations of cTn values are common in patients in the intensive care unit and are associated with adverse prognosis regardless of the underlying disease state.^{107,108} Some elevation of cTn values may reflect type 2 MI due to underlying CAD and increased myocardial oxygen demand,¹⁰⁹ whereas in other patients, type 1 MI may occur because of plaque disruption leading to thrombosis in a coronary artery. However, other patients may have elevated cTn values and marked decreases in EF due to sepsis caused by endotoxin, with myocardial function recovering completely with normal EF once the sepsis is treated. It is frequently challenging for the clinician caring for a critically ill patient with a severe single organ or multiorgan pathological condition to decide on a plan of action when the patient has elevated cTn values. If and when the patient recovers from the critical illness, clinical judgement should be employed to decide whether, and to what extent, further evaluation for CAD or structural heart disease is indicated.¹¹⁰

23 Biochemical approach for diagnosing myocardial injury and infarction

cTnI and cTnT are the preferred biomarkers recommended to both rule in and rule out myocardial injury, and thus to define MI and each specific subtype of MI.^{12,22,23,31} Detection of a rise and/or fall of cTn values is essential, and a key early component along with other

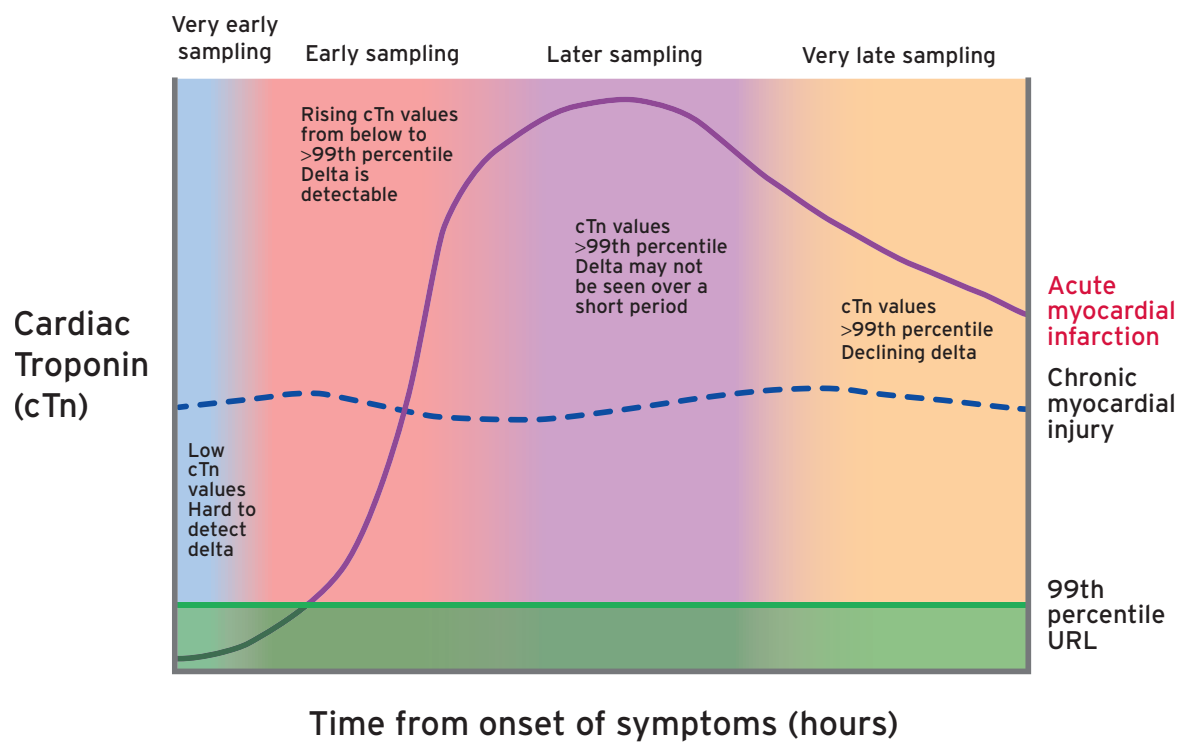


Figure 7 Illustration of early cardiac troponin kinetics in patients after acute myocardial injury including acute myocardial infarction. The timing of biomarker release into the circulation is dependent on blood flow and how soon after the onset of symptoms samples are obtained. Thus, the ability to consider small changes as diagnostic can be problematic. In addition, many comorbidities increase cTn values and, in particular, hs-cTn values, so that elevations can be present at baseline even in those with myocardial infarction who present early after the onset of symptoms. Changes in cTn values or deltas can be used to define acute compared with chronic events, and the ability to detect these is indicated in the figure. Increased cTn values can often be detected for days after an acute event. cTn = cardiac troponin; URL = upper reference limit.

elements of the clinical evaluation to establish the diagnosis of acute MI. Criteria for determining a pathological rise between two serial cTn values are assay-dependent and continue to evolve. An idealized view of troponin kinetics in patients with acute MI is shown in Figure 7.

It should be appreciated that because biomarker release is substantially dependent on blood flow,^{111,112} there is significant variability in the time to peak value (velocity), the time when a normal value may become greater than the 99th percentile URL, or when a changing pattern of values can be observed. The ability to define a changing pattern will also depend on timing. For example, around peak values, it may be difficult to observe a changing pattern of values. Similarly, the downslope of the time–concentration curve is much slower than the upslope. These issues need to be taken into account when defining whether or not a changing pattern is present. In addition, it is important to make sure that a given change is greater than can be anticipated by variability alone. This is defined for conventional cTn assays as a change greater than or equal to three times the standard

deviation around the measurement of the individual assay at relevant values.^{12,22} For hs-cTn assays, biological variation also needs to be considered. In most studies, conjoint analytical and biological variation is in the range of 50–60%.

For that reason, this percentage has been suggested for use when initial baseline values are \leq the 99th percentile URL.^{23,31,113} However, for individuals with an initial value greater than the 99th percentile URL, a lesser degree of change during serial measurements is necessary to achieve improved clinical sensitivity (as compared with individuals with initial values \leq the 99th percentile URL). Thus, an expert consensus group has recommended serial changes $> 20\%$ be used in this situation.²² Absolute changes are assay dependent but appear superior to relative per cent changes with hs-cTn assays,¹¹⁴ and in some studies this is especially the case when the initial value is increased.¹¹⁵ The use of a fixed absolute value change criteria translates into a smaller percentage or relative change as absolute values rise, and therefore provides greater sensitivity. The use of a changing pattern is important in allowing clinicians to differentiate an acute

from a chronic cTn increase above the 99th percentile URL.^{113–115} Using criteria less than conjoint analytical and biological variation will reduce the clinical specificity of hs-cTn assays.^{113,116} An imprecision of $\leq 10\%$ coefficient of variation (CV) at the 99th percentile URL is also mandatory for hs-cTn assays.³¹ The use of non-hs-cTn assays that do not have imprecision ($\leq 10\%$ CV at the 99th percentile URL) makes the determination of a significant serial change more difficult but does not cause false positive results. Assays with CVs between 10–20% are acceptable for clinical use. However, assays with CVs $> 20\%$ at the 99th percentile URL should not be used.¹¹⁷

If a cTn assay is not available, the best alternative is CK-MB measured by a mass assay. As with cTn, an increased CK-MB value is defined as a measurement above the 99th percentile URL, which is designated as the decision level for the diagnosis of MI. Sex-specific CK-MB values should be employed.¹¹⁸

24 Analytical issues of cardiac troponins

The analytical sensitivity [limit of detection (LoD)] of cTnI and cTnT assays varies 10-fold.^{31,119} Because assays are not standardized, values from one assay cannot be directly compared with those from another assay. Furthermore, values may be different between assay generations¹²⁰ and changes can even occur when the same assay reagents are measured on different instruments.¹²¹ Thus, clinicians must learn about their local assay and should look for reliable information, e.g. available on the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) website (<http://www.ifcc.org/executive-board-and-council/eb-task-forces/task-force-on-clinical-applications-of-cardiac-bio-markers-tf-cb/>), when they have questions concerning analytical issues. The current guidelines accommodate all assays, whether hs-cTn, contemporary (conventional) cTn, or point of care (POC) cTn. While hs-cTn assays are able to measure relatively low values and document small increases above the 99th percentile URL, many contemporary and POC cTn assays may not detect small increasing values within the reference interval or slightly above the 99th percentile URL, leading to substantial differences in the frequency of events based solely on the cTn assay used. These differences are amplified when multiples of the 99th percentile URL are used. At present, IFCC guidelines support the concept that hs-cTn assays are differentiated from contemporary or POC cTn assays by their ability to measure cTn values above the assay's LoD in $\geq 50\%$ of healthy individuals.^{31,118,119,122} This provides a rough estimate of assay sensitivity. It is recommended that values for cTn assays be reported as whole numbers in nanograms per litre to avoid interpretation problems associated with multiple zeros and decimal points that can often result in confusion.³¹ Clinicians should avoid mixing the units from contemporary assays with those from hs-cTn assays. All assays, including cTn assays, have some analytical problems resulting in false positive and false negative results, but these are uncommon ($< 0.5\%$).²² These problems are less common with hs-cTn assays.²³

Conjoint biological and analytical variation of hs-cTn assays is in the range of 50–60%.¹²³ When values are elevated, analytical variation is less and a value of 20% can be used to determine that values are stable in the proper clinical context. For example, changes may

be difficult to observe over short periods of time in those who present early after the onset of symptoms of acute MI, those who present late and are on the downslope of the time-concentration curve, and those who have values near peak where they may be transitioning from a rising to a falling pattern.^{113,123}

25 The 99th percentile upper reference limit

The 99th percentile URL is designated as the decision level for the presence of myocardial injury and must be determined for each specific assay with quality control materials used at the URL to validate appropriate assay imprecision. The cTn assay 99th percentile URL values used in clinical practice and research can be found both in manufacturers' package inserts, in peer-reviewed publications, and on the IFCC website.^{118–120} Clinicians should be aware that for all cTn assays, including hs-cTn assays, there is still no expert opinion or consensus about specific criteria for how the 99th percentile URL should be defined.¹²⁴ We endorse IFCC guidelines on the technical issues related to hs-cTn assays, including how studies should be configured to determine 99th percentile URLs.¹¹⁹ The guidelines include the clinical or surrogate biomarker screening that may be needed to better define the 99th percentile URL and the statistical methods that can be applied, but do not include a requirement for cardiac imaging.¹¹⁹ Screening of apparently healthy subjects with imaging has been shown to lower the observed 99th percentile URL value, but is not a practical standard for the *in vitro* diagnostic industry to use.^{124,125} Thus, there is the possibility of false negative values using the manufacturer's reported 99th percentile URL values. hs-cTn assays demonstrate shifts to higher values for the 99th percentile URL in association with comorbidities and age over > 60 years.^{101,125–127} However, at present, age-dependent cut-off points are not recommended for clinical use. Clinicians should rely instead on changing values during serial measurements of cTn for the diagnosis of acute myocardial injury, including MI. Significantly lower values are observed among women compared with men, and therefore sex-specific 99th percentile URLs are recommended for hs-cTn assays.^{31,118–120} For some hs-cTn assays, sex-specific cut-off values have been reported to improve diagnostic and prognostic information in patients with possible acute MI.^{128,129} However, there is controversy as to whether this approach provides valuable additional information for all hs-cTn assays.¹³⁰

26 Operationalizing criteria for myocardial injury and infarction

Blood samples for the measurement of cTn should be drawn on first assessment (designated as 0 h) and repeated 3–6 h later, or earlier with hs-cTn assays. The sampling interval will impact the clinical cut-off at baseline and what is determined to be a pathological rise and/or fall of the biomarker. Sampling beyond 6 h may be required if further ischaemic episodes occur, or in high-risk patients. To establish the diagnosis of an acute MI, a rise and/or fall in cTn values with at least one value above the 99th percentile URL is required, coupled with a high clinical and/or ECG likelihood of myocardial ischaemia. hs-cTn

assays shorten the time to diagnosis in many patients to within 3 h of onset of symptoms, but there are still some patients who may rule in late (at 6 h).¹³¹ Furthermore, some patients with acute myocardial injury presenting late after the onset of acute MI (> 12–18 h) and who are on the downslope of the time-concentration curve may require longer periods of time for a changing pattern to be detected.¹³¹ In addition, it should be noted that with the implementation of cTn and hs-cTn assays, the frequency of unstable angina will decrease and the diagnosis of NSTEMI will increase.^{132,133} The magnitude of these changes using hs-cTn assays have been reported in the range of 18–30%.¹³⁴ Assuming proper timing of symptoms, acute ischaemia should result in a change in hs-cTn; however, there may be patients in whom it is difficult to ascertain the timing of symptom onset. Thus, despite typical chest discomfort, these patients may have hs-cTn values that are not elevated. Other patients with symptoms suggestive of unstable angina may have increased hs-cTn values as a result of structural heart disease with or without acute myocardial ischaemia. This latter group may be particularly difficult to distinguish from patients presenting with late NSTEMI with a slow decline in troponin values that can be observed in late presenters.¹³¹ Finally, some patients may manifest a changing pattern of troponin values with a magnitude that does not exceed the delta suggested for diagnosis or who fail to manifest a value greater than the 99th percentile URL. This is a group of patients that deserves close scrutiny because they may be at high risk. The triage of these patients can only be accomplished based on clinical evaluation.

Strategies employing either very low levels of hs-cTn on presentation or the lack of any change and persistently normal hs-cTn values over a 1–2 h period after presentation have been advocated to exclude acute myocardial injury, and MI as well. A single sample rule out strategy using a very low value (in many cases the LoD of the assay) has high sensitivity for myocardial injury and therefore high negative predictive value to exclude MI.¹³⁵ This strategy should not be used in those who present early, i.e. < 2 h after the onset of chest discomfort. Some studies indicate that the single sample approach provides optimal sensitivity and negative predictive accuracy in patients otherwise at low risk and those with a normal ECG.^{136–138} However, one concern about very short rule out periods is that the precision of the assays may not permit small differences to be distinguished.^{139–142} These criteria have not, and should not, be applied to patients with hs-cTn elevations.

The clinical specificity and positive predictive value of such 1–2 h sampling approaches for ruling in MI are limited by the substantial proportion of individuals who meet the proposed biomarker criteria with diagnoses other than MI.^{136,141} Thus, the use of a rapid rule in/out MI protocol does not absolve the clinician from considering other causes of acute myocardial injury.¹⁴² In addition, considering a broader population of patients—inclusive of those who present atypically, those with end-stage renal disease, and the critically ill—the cut-off points to be used will likely need to be altered.¹³⁹ Such patients have been excluded from the majority of emergency department evaluation studies.^{108,136,142}

The demonstration of a rising and/or falling pattern is needed to distinguish acute injury from chronic conditions associated with structural heart disease that can have chronic increases of cTn values. For example, patients with renal failure^{99,143,144} or LV hypertrophy¹⁴⁵ can have significant chronic increases in cTn values. These increases

can be marked but do not change acutely during serial sampling. However, a falling pattern may take longer to be observed in patients with a high pre-test risk of MI who present late after symptom onset.¹⁴⁶ These patients who have cTn values on the downslope of the time-concentration curve have a slow decline in values (Figure 7). Thus, detecting a changing pattern over short periods of time may be difficult.¹¹⁷ Depending on the extent of myocardial injury, cTn values may remain above the 99th percentile URL for a longer period of time.^{22,23} An increased cTn value above the 99th percentile URL, with or without a dynamic change of values, or in the absence of clinical evidence of ischaemia, should prompt a search for other diagnoses associated with myocardial injury, as shown in Table 1.

27 Electrocardiographic detection of myocardial infarction

The ECG is an integral part of the diagnostic workup of patients with suspected MI, and should be acquired and interpreted promptly (i.e. target within 10 min) after first medical contact.^{47,147} Pre-hospital ECGs reduce the time to diagnosis and treatment, and can facilitate the triage of STEMI patients to hospitals with PCI capability if within the recommended time interval (120 min from STEMI diagnosis).^{46,148} Acute myocardial ischaemia is often associated with dynamic changes in ECG waveform and serial ECG acquisition can provide critical information, particularly if the ECG at initial presentation is non-diagnostic. Recording several standard ECGs with fixed electrode positions at 15–30 min intervals for the initial 1–2 h, or the use of continuous computer-assisted 12-lead ECG recording (if available) to detect dynamic ECG changes, is reasonable for patients with persistent or recurrent symptoms or an initial non-diagnostic ECG.¹⁴⁹ Serial or continuous ECG recordings may be helpful in determining reperfusion or reocclusion status. Reperfusion is usually associated with a large and prompt reduction in ST-segment elevation.

More profound ST-segment shifts or T wave inversions involving multiple leads/territories are associated with a greater degree of myocardial ischaemia, and a worse prognosis. For example, ST-segment depression ≥ 1 mm in six leads, which may be associated with ST-segment elevation in leads aVR or lead V₁ and haemodynamic compromise, is suggestive evidence of multivessel disease or left main disease. Pathologic Q waves increase the prognostic risk. Other ECG signs associated with acute myocardial ischaemia include cardiac arrhythmias, intraventricular bundle branch blocks, atrioventricular conduction delays, and loss of precordial R wave amplitude, a less specific finding. The ECG by itself is often insufficient to diagnose acute myocardial ischaemia or infarction, since ST deviation may be observed in other conditions, such as acute pericarditis, LV hypertrophy (LVH), left bundle branch block (LBBB), Brugada syndrome, TTS, and early repolarization patterns.¹⁵⁰ A prior ECG is often helpful in distinguishing a new from a chronic finding, but should not delay the decision for treatment.

Prolonged new convex ST-segment elevation, particularly when associated with reciprocal ST-segment depression, usually reflects acute coronary occlusion and results in myocardial injury with necrosis. Reciprocal changes can help to differentiate STEMI from pericarditis or early repolarization changes. As in cardiomyopathy, Q waves may also occur due to myocardial fibrosis in the absence of

CAD. Some of the earlier manifestations of myocardial ischaemia are typical T wave and ST-segment changes. Increased hyperacute T wave amplitude, with prominent symmetrical T waves in at least two contiguous leads, is an early sign that may precede the elevation of the ST-segment. In general, the development of new Q waves indicates myocardial necrosis, which starts minutes/hours after the myocardial insult. Transient Q waves may be observed during an episode of acute ischaemia or (rarely) during acute MI with successful reperfusion. Table 2 lists ST-segment–T wave (ST-T) criteria suggestive of acute myocardial ischaemia that may or may not lead to MI. The J-point (junction between QRS termination and ST-segment onset) is used to determine the magnitude of the ST-segment shift with the

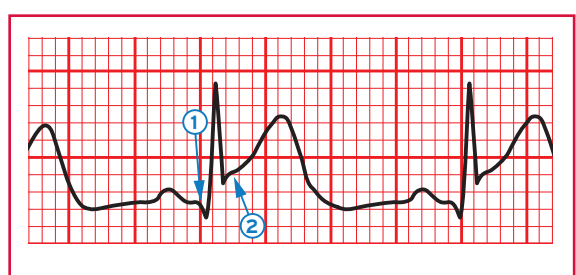


Figure 8 Electrocardiogram example of ST-segment elevation. The initial onset of the Q wave shown by arrow 1 serves as the reference point and arrow 2 shows the onset of the ST-segment or J-point. The difference between the two identifies the magnitude of displacement. Measurements of both arrows should be made from the top of the electrocardiogram line tracing.

Table 2 Electrocardiographic manifestations suggestive of acute myocardial ischaemia (in the absence of left ventricular hypertrophy and bundle branch block)

ST-elevation
New ST-elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V_2 – V_3 where the following cut-points apply: ≥ 2 mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age. ^a
ST-depression and T wave changes
New horizontal or downsloping ST-depression ≥ 0.5 mm in two contiguous leads and/or T inversion > 1 mm in two contiguous leads with prominent R wave or R/S ratio > 1 .

^aWhen the magnitudes of J-point elevation in leads V_2 and V_3 are registered from a prior electrocardiogram, new J-point elevation ≥ 1 mm (as compared with the earlier electrocardiogram) should be considered an ischaemic response. For bundle branch block, see section below.

onset of the QRS serving as the reference point. In patients with a stable baseline, the TP segment (isoelectric interval) is a more accurate method to assess the magnitude of ST-segment shift, and in distinguishing pericarditis (PTa depression) from acute myocardial ischaemia. Tachycardia and baseline shift are common in the acute setting and can make this determination difficult. Therefore, QRS onset is recommended as the reference point for J-point determination (Figure 8).

New, or presumed new, J-point elevation ≥ 1 mm (1 mm = 0.1 mV) is required in all leads other than V_2 and V_3 as an ischaemic response. In healthy men under age 40, J-point elevation can be as much as 2.5 mm in leads V_2 or V_3 , but it decreases with increasing age. Sex differences require different cut-off points for women, since J-point elevation in healthy women in leads V_2 and V_3 is less than in men.⁵ The criteria in Table 2 require that the ST shift be present in two or more contiguous leads. For example, ≥ 2 mm of ST-elevation in lead V_2 and ≥ 1 mm in lead V_1 would meet the criteria of two abnormal contiguous leads in a man ≥ 40 years old. However, ≥ 1 mm and < 2 mm of ST-elevation, seen only in leads V_2 – V_3 in men (or < 1.5 mm in women), may represent a normal finding.

It should be noted that lesser degrees of ST displacement or T wave inversion than those described in Table 2 can also represent an acute myocardial ischaemic response. In patients with known or high likelihood of CAD, the clinical presentation is critical to enhance the specificity of these findings.

Absence of ST-elevation in the precordial leads, tall, prominent, symmetrical T waves in the precordial leads, upsloping ST-segment depression > 1 mm at the J-point in the precordial leads, and in most cases ST-segment elevation (> 1 mm) in lead aVR or the symmetrical, often deep (> 2 mm), T wave inversions in the anterior precordial leads are associated with significant left anterior descending artery (LAD) occlusion.^{151–153} ST-elevation in lead aVR > 1 mm may accompany anterior or inferior STEMI, and is associated with increased 30 day mortality in patients with acute MI.¹⁵⁴ Pulmonary embolism, intracranial processes, electrolyte abnormalities, hypothermia, or perimyocarditis may also result in ST-T abnormalities and should be considered in the differential diagnosis.

The ECG diagnosis of atrial infarction should be suspected in the context of ventricular infarction (particularly when the right ventricle is involved) if small, transient elevations and reciprocal depressions of the PR (PTa) segment are noted associated with changes in configuration of the P wave.

28 Application of supplemental electrocardiogram leads

Supplemental leads, as well as serial ECG recordings, should be deployed with a very low threshold in patients who present with ischaemic chest pain and a non-diagnostic initial ECG.^{155,156} ECG evidence of myocardial ischaemia in the distribution of a left circumflex artery is often overlooked. Isolated ST-segment depression ≥ 0.5

mm in leads V_1 – V_3 may indicate left circumflex occlusion and can best be captured using posterior leads at the fifth intercostal space (V_7 at the left posterior axillary line, V_8 at the left mid-scapular line, and V_9 at the left paraspinous border). Recording of these leads is strongly recommended in patients with high clinical suspicion of acute circumflex occlusion (e.g. initial ECG non-diagnostic or ST-segment depression in leads V_1 – V_3).¹⁵⁶ A cut-off point of 0.5 mm ST-elevation is recommended in leads V_7 – V_9 ; specificity is increased at a cut-off point ≥ 1 mm ST-elevation and this cut-off point should be used in men < 40 years old. ST-segment depression in leads V_1 – V_3 may be suggestive of inferobasal myocardial ischaemia (previously termed posterior infarction), especially when the terminal T wave is positive (ST-elevation equivalent); however, this is non-specific.

In patients with inferior and suspected right ventricular infarction, leads aVR or V_1 may exhibit ST-segment elevation ≥ 1 mm. The early recording of right precordial leads V_3R and V_4R should be performed, since ST-elevation ≥ 0.5 mm (≥ 1 mm in men < 30 years old) provides supportive criteria for the diagnosis.¹⁵⁷ Changes in right precordial leads may be transient, and an absence of ECG changes in leads V_3R and V_4R does not exclude right ventricular infarction. Myocardial imaging can be helpful in this clinical setting.

29 Electrocardiographic detection of myocardial injury

It is not possible to initially distinguish ECG manifestations of acute or chronic myocardial injury from acute myocardial ischaemia. Rapidly developing dynamic ECG changes that temporally match the clinical presentation may be helpful in diagnosing a symptomatic patient with elevated cTn values as having acute myocardial ischaemia resulting in MI. However, ECG abnormalities are also common in patients who have myocardial injury, e.g. myocarditis or TTS.^{158–160}

30 Prior or silent/unrecognized myocardial infarction

Q wave criteria associated with MI and an increased relative risk of death are illustrated in Table 3, and are contained in Q wave coding algorithms such as the Minnesota Code and the WHO MONItoring of trends and determinants in CArdiovascular disease (MONICA) code.^{11,161,162}

The specificity of the ECG diagnosis for MI is greatest when Q waves occur in several leads or lead groupings, or are > 0.04 s. When the Q waves are associated with ST deviations or T wave changes in the same leads, the likelihood of MI is increased; for example, minor Q waves ≥ 0.02 s and < 0.03 s that are ≥ 1 mm deep are suggestive of prior MI if accompanied by inverted T waves in the same lead group. Non-invasive imaging techniques also provide important supportive evidence of prior MI. In the absence of non-ischaemic causes, regional myocardial thinning, scar or reduced wall motion shown by echocardiography, myocardial perfusion scintigraphy (MPS) with single photon emission computed tomography (SPECT) or positron emission tomography (PET), or magnetic resonance imaging provide strong evidence for prior MI, particularly when ECG criteria are equivocal.

Table 3 Electrocardiographic changes associated with prior myocardial infarction (in the absence of left ventricular hypertrophy and left bundle branch block)

Any Q wave in leads V_2 – V_3 > 0.02 s or QS complex in leads V_2 – V_3 .	©ESC/ACC/AHA/WHF 2018
Q wave ≥ 0.03 s and ≥ 1 mm deep or QS complex in leads I, II, aVL, aVF or V_4 – V_6 in any two leads of a contiguous lead grouping (I, aVL; V_1 – V_6 ; II, III, aVF). ^a	
R wave > 0.04 s in V_1 – V_2 and R/S > 1 with a concordant positive T wave in absence of conduction defect.	

^aThe same criteria are used for supplemental leads V_7 – V_9 , s = seconds.

Asymptomatic patients who develop new Q wave criteria for MI detected during routine ECG follow-up, or reveal evidence of MI by cardiac imaging that cannot be directly attributed to an interim coronary revascularization procedure or an ACS admission, should be termed 'silent or unrecognized MI'. In studies where serial ECG analysis was applied, silent or unrecognized Q wave MI accounted for 9–37% of all non-fatal MI events and was associated with a significantly increased mortality risk.^{163,164} Improper lead placement, QRS abnormalities, or technical errors (e.g. lead reversal) may result in the appearance of new Q waves or QS complexes, as compared with a prior tracing. Thus, the diagnosis of a new silent Q wave MI should be confirmed by a repeat ECG recording with correct lead placement, focused questioning about potential interim ischaemic symptoms, or by an imaging study. Imaging techniques are useful if there is abnormal myocardial motion, thickening, or thinning in the region of interest, but the absence of these does not exclude MI.¹⁶⁵

Criteria for prior or silent/unrecognized MI

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Pathological Q waves as described in Table 3, with or without symptoms, in the absence of non-ischaemic causes;
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology;
- Pathological findings of a prior MI.

31 Conditions that confound the electrocardiographic diagnosis of myocardial infarction

A QS complex in lead V_1 is normal. A Q wave < 0.03 s and < 0.25 of the R wave amplitude in lead III is normal if the frontal QRS axis is between -30° and 0° . A Q wave may also be normal in aVL if the

frontal QRS axis is between 60–90°. Septal Q waves are small, non-pathological Q waves < 0.03 s and < 0.25 of the R-wave amplitude in leads I, aVL, aVF, and V₄–V₆. Pre-excitation, cardiomyopathy, TTS, cardiac amyloidosis, LBBB, left anterior hemiblock, LVH, right ventricular hypertrophy, myocarditis, acute cor pulmonale, or hyperkalaemia may be associated with Q waves or QS complexes in the absence of MI. Clinicians should be aware of confounders to the ECG diagnosis of myocardial ischaemia, since ST-T wave abnormalities are commonly observed with different pathological cardiac conditions, such as pre-excitation, pericarditis, and cardiomyopathy.

32 Conduction disturbances and pacemakers

The diagnosis of MI is more difficult in the presence of conduction disturbances, related in part to ST-T wave changes caused by the conduction disturbance and the fact that the conduction disturbance itself may be heart-rate dependent.^{166,167} Comparison to a pre-admission ECG may be helpful in determining if the conduction defect or ST-T wave changes are new, as long as it does not delay time to treatment. Ischaemic symptoms, and presumed new LBBB or right bundle branch block (RBBB) that is not rate-related, are associated with an adverse prognosis. In patients with LBBB, ST-segment elevation ≥ 1 mm concordant with the QRS complex in any lead may be an indicator of acute myocardial ischaemia. Similar findings can be useful in detecting ECG evidence for acute myocardial ischaemia in patients with right ventricular paced rhythms.¹⁶⁷ Recording an ECG trace with the pacemaker temporarily switched off may also be useful in patients who are not pacemaker dependent, but careful interpretation of repolarization is needed due to the possible presence of stimulation-induced changes (electrical memory). The ECG diagnosis of acute myocardial ischaemia in patients with biventricular pacing is more difficult. In patients with RBBB, new or presumed new ST-segment elevation ≥ 1 mm, or ST-segment or T wave abnormalities (excluding leads V₁–V₄) (Table 2), may indicate acute myocardial ischaemia. New, or presumed new, RBBB without associated ST-segment or T wave changes is associated with thrombolysis in myocardial infarction (TIMI) 0–2 flow in as many as 66% of patients (compared with > 90% in those with ST-segment or T wave changes).¹⁶⁸

33 Atrial fibrillation

In patients with atrial fibrillation and rapid ventricular rate or paroxysmal supraventricular tachycardia, ST-segment depression or T wave inversion may occur in the absence of CAD.^{169,170} The causes are not completely understood. Cardiac memory, an electrical remodeling phenomenon characterized by marked diffuse T wave inversions following periods of abnormal ventricular activation, which may also be caused by transient rate-related conduction disturbances or pacing, may explain these findings. In some patients, the tachycardia may result in an insufficient increase in coronary flow to match myocardial oxygen demand, resulting in cellular hypoxia and abnormal repolarization.^{171,172} For these reasons, a patient with new-onset atrial fibrillation, elevated baseline cTn concentration, and new ST-segment

depression should not automatically be classified as type 2 MI without additional information. In this clinical setting, signs of overt ischaemic symptoms, the timing of symptoms relative to atrial fibrillation onset, a changing pattern of cTn, and imaging and/or angiographic findings may be helpful in establishing the diagnosis. However, in the absence of evidence for myocardial ischaemia, the aetiology of the elevated cTn values should be attributed to myocardial injury.

34 Imaging techniques

Non-invasive imaging plays many roles in patients with known or suspected MI, but this section concerns only its role in the diagnosis and characterization of myocardial injury and MI. The underlying rationale is that regional myocardial hypoperfusion and ischaemia lead to a cascade of events including myocardial dysfunction, cell death, and healing by fibrosis. Important imaging parameters are therefore myocardial perfusion, myocyte viability, myocardial thickness, thickening and motion, and the effects of myocyte loss on the kinetics of paramagnetic or radio-opaque contrast agents indicating myocardial fibrosis or scar.

Commonly used imaging techniques in acute and prior MI are echocardiography, MPS using SPECT or PET, CMR, and possibly computed tomography (CT).¹⁷³ There is considerable overlap in their capabilities and each of the techniques can assess myocardial viability, perfusion, and function to a greater or lesser extent. Only the radionuclide techniques provide a direct assessment of myocyte viability because of the inherent properties of the tracers used. Other techniques provide indirect assessments of myocardial viability, such as the contractile response to dobutamine by echocardiography, or increased extracellular space secondary to myocyte loss by CMR or CT.

34.1 Echocardiography

The strength of echocardiography is the combined assessment of cardiac structure and function, in particular myocardial thickness, thickening/thinning, and motion. Regional wall motion abnormalities induced by ischaemia can be detected by echocardiography almost immediately after onset when > 20% transmural myocardial thickness is affected.^{174–176} These abnormalities, when new and without alternative aetiology, support the diagnosis of MI when cTn values show a rising and/or falling pattern. Echocardiography also allows detection of non-coronary cardiac pathologies known to cause chest pain, e.g. acute pericarditis, severe aortic stenosis, and hypertrophic cardiomyopathy among others. The technique is useful in diagnosing mechanical complications in patients with MI and haemodynamic compromise (shock), or other potentially fatal entities such as acute aortic dissection or massive pulmonary embolism where the clinical presentation might be similar to that seen with acute MI.

Intravenous echocardiographic contrast agents can improve visualization of the endocardial border, and can be used to assess myocardial perfusion and microvascular obstruction. Tissue Doppler and strain imaging permit the quantification of global and regional function.^{177,178} Intravascular echocardiographic contrast agents that are targeted at specific molecular processes have been developed, but these techniques have not yet been applied in the setting of MI.¹⁷⁹

34.2 Radionuclide imaging

Several radionuclide tracers allow viable myocytes to be imaged directly, including the SPECT tracers ^{201}Tl chloride, $^{99\text{m}}\text{Tc}$ sestamibi, and tetrofosmin, and the PET tracers ^{18}F 2-fluorodeoxyglucose and ^{82}Rb .¹⁷³ A strength of the radionuclide techniques is that they are the only commonly available methods for assessing viability directly, although the relatively low resolution of the images limits them for detecting the smallest areas of MI. Phantom studies suggest that myocyte loss as little as 4% of the myocardium can be detected, corresponding to 5–10 g of muscle.¹⁸⁰ ECG-gated imaging provides a reliable assessment of myocardial motion, thickening, and global function. Evolving radionuclide techniques relevant to the assessment of MI include imaging of sympathetic innervation using ^{123}I -labelled

meta-iodobenzylguanidine,¹⁸¹ imaging of matrix metalloproteinase activation in ventricular remodelling,^{182,183} and the assessment of myocardial metabolism.¹⁸⁴

34.3 Cardiac magnetic resonance imaging

The high tissue contrast and resolution of CMR provides an accurate assessment of myocardial structure and function. Although less commonly used in the acute setting, it has similar capabilities to echocardiography in suspected MI. Paramagnetic contrast agents can be used to assess myocardial perfusion and the increase in extracellular space that is associated with the fibrosis of prior MI (detected by LGE-CMR). These techniques have been used in the setting of acute

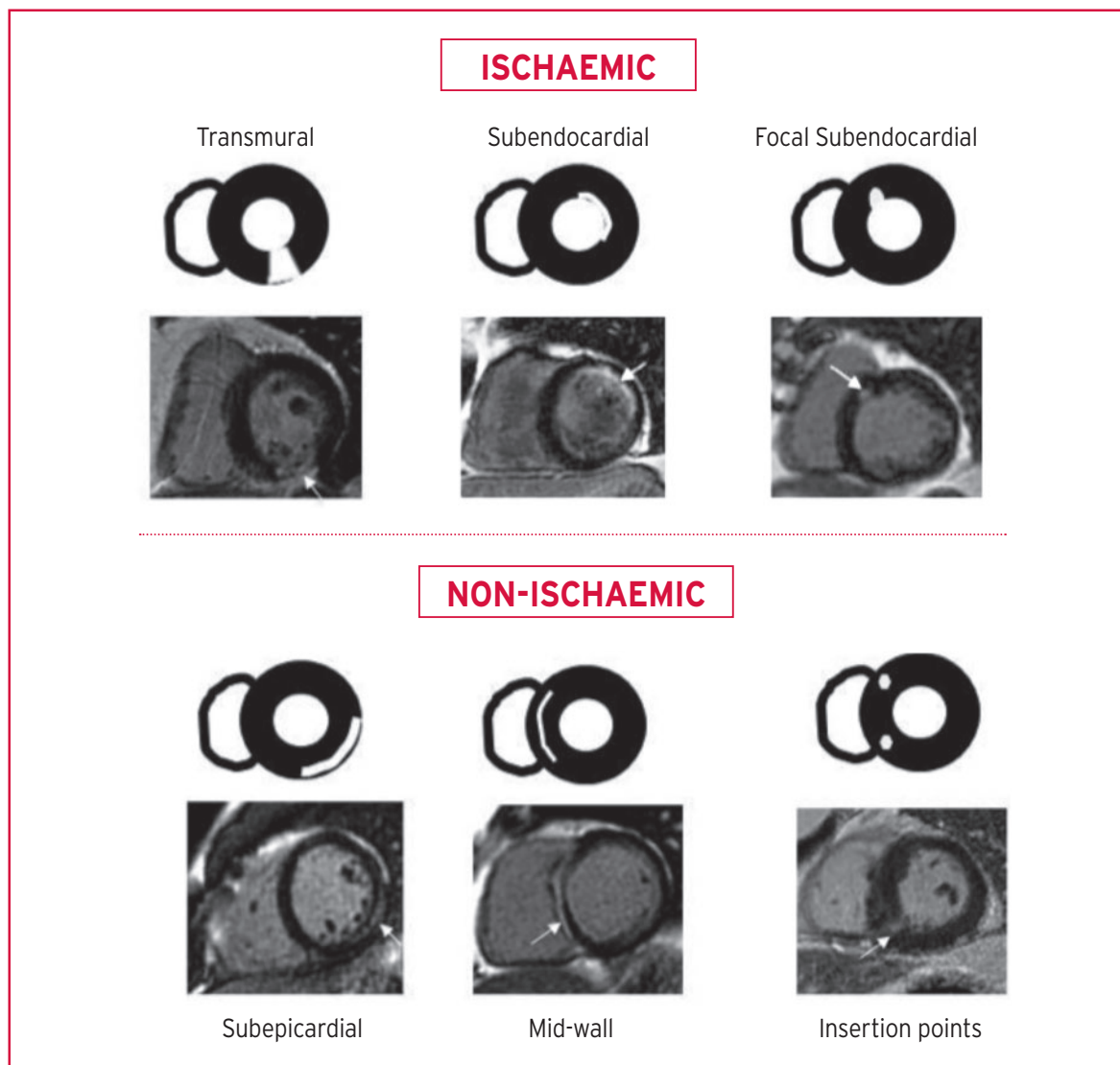


Figure 9 Post-contrast cardiac magnetic resonance images. The gadolinium-based contrasts wash out slowly from myocardium with increased extracellular space such as fibrosis, thus enhancing areas of scarring (white arrows). The different patterns of scarring are divided into ischaemic and non-ischaemic. Typically, an ischaemic scar/fibrosis (upper panel) extends from the subendocardium to the epicardium (subendocardial, non-transmural scar vs. transmural scar). Conversely, a non-ischaemic fibrosis/scar can be encountered at the epicardium, in the mid-wall, or at the insertion points of the right ventricle (lower panel).

MI^{185,186} and localized delay in contrast enhancement is able to detect even small areas of subendocardial MI, thought to be as little as 1 g.¹⁸⁷ CMR also has the ability to identify the presence and extent of myocardial oedema/inflammation, allowing the distinction of acute vs. chronic myocardial injury. The patterns of LGE when reflecting ischaemic and non-ischaemic myocardial injury are shown in *Figure 9*.

The gadolinium-based contrasts wash out slowly from myocardium with increased extracellular space such as fibrosis, thus enhancing areas of scarring (white arrows). The different patterns of scarring are divided into ischaemic and non-ischaemic. Typically, an ischaemic scar/fibrosis (upper panel) extends from the subendocardium to the epicardium (subendocardial, non-transmural scar vs. transmural scar). Conversely, a non-ischaemic fibrosis/scar can be encountered at the epicardium, in the mid-wall, or at the insertion points of the right ventricle (lower panel).

34.4 Computed tomographic coronary angiography

Infarcted myocardium is initially visible as a focal area of decreased LV myocardial enhancement, but later imaging shows hyper-enhancement as with LGE-CMR.¹⁸⁸ This finding is clinically relevant because contrast-enhanced CT may be performed for suspected pulmonary embolism and aortic dissection, conditions with clinical features that overlap with those of acute MI, but the technique is not used routinely. Similarly, CT assessment of myocardial perfusion is technically feasible but not widely applied.¹⁸⁹ CT coronary angiography (CTCA) may be used to diagnose CAD in patients with an ACS in the emergency department or chest pain unit, particularly in low- to intermediate-risk patients with normal cTn at presentation.^{189–193} The only randomized trial in these patients that included both hs-cTn and CTCA found that imaging did not reduce the length of stay in hospital, but it did decrease subsequent outpatient testing and costs.¹⁸⁹ A diagnosis of MI cannot be established based on a CTCA scan alone.

35 Applying imaging in acute myocardial infarction

Imaging techniques can be useful in the diagnosis of acute MI because of the ability to detect wall motion abnormalities or loss of viable myocardium in the presence of elevated cardiac biomarker values. Demonstration of new loss of myocardial viability in the absence of non-ischaemic causes supports the diagnosis of MI. Normal function practically excludes significant MI, but a small MI cannot be ruled out.¹⁹⁴ Thus, imaging techniques are useful for early triage and discharge of patients with suspected MI. However, if biomarkers have been measured at appropriate times and are normal, this excludes acute MI and takes precedence over the imaging criteria.

Abnormal regional myocardial motion and thickening may be caused by acute MI, or by one or more of several other conditions including prior infarction, acute ischaemia, stunning, or hibernation. Non-ischaemic conditions such as cardiomyopathy, and inflammatory or infiltrative diseases, can also lead to regional loss of viable myocardium or functional abnormality. Therefore, the positive predictive value of imaging for acute MI is not high unless these conditions can

be excluded, and unless a new abnormality is detected or can be presumed to have arisen in the setting of other features of acute MI.

In the setting of acute MI, CMR can also be used to assess the presence and extent of myocardium at risk (myocardial oedema), myocardial salvage, microvascular obstruction, intramyocardial haemorrhage, and infarct size, all markers of myocardial injury that have prognostic value.¹⁹⁰ In patients with possible acute MI but unobstructed coronary arteries, CMR can help to diagnose alternative conditions such as myocarditis, TTS, embolic infarction, or MI with spontaneous recanalization.¹⁸⁹

36 Applying imaging in late presentation of myocardial infarction

In the case of late presentation after suspected MI, the presence of a regional abnormality of myocardial motion, thickening, thinning, or scar in the absence of a non-ischaemic cause provides supportive evidence of past MI. The resolution and specificity of CMR for the detection of myocardial scarring has made this a valuable technique. In particular, the ability to distinguish between subendocardial and other patterns of scars helps to differentiate between ischaemic heart disease and other myocardial pathologies. Imaging techniques are also useful for risk stratification after a definitive diagnosis of MI.

37 Regulatory perspective on myocardial infarction in clinical trials

In drug and device development programmes, MI may be an entry criterion or be used as an efficacy endpoint, commonly as a component of the primary endpoint, as well as a safety endpoint of interest in drug development programmes.^{195,196} A universal definition of MI is of great benefit for clinical studies, since it will allow a standardized approach for meaningful interpretation and comparison across different trials, or the pooling of results for the detection of safety signals. For the harmonization of the MI definition it is important to standardize the reporting of MI events by clinical events committees. This would allow a more optimal comparison of MI rates among drug and device trials.

One cannot presume that values from one cTn assay are equivalent to those of another. These differences are amplified when multiples of the values are used. This could affect results, especially in trials that compare strategies such as PCI and CABG. The use of one single assay and/or a central core laboratory within a trial could help to decrease this variability, and might be particularly relevant in decreasing variability in trials of a drug or intervention in which cTn concentration is a principal safety endpoint. However, the uniform use of a single assay is generally not feasible in trials with follow-up post-discharge, since recurrent ischaemic events may occur in different hospitals using different cTn assays. In clinical trials, a standardized approach to establish the 99th percentile URL for a particular assay should be established. One approach in large multicentre trials is to use the manufacturer's recommended 99th percentile URL for a

particular assay to reduce site-to-site variability in the selection of the MI decision cut-off point.

Multiples for hs-cTn vs. conventional cTn could have markedly different prognostic implications. The assay types should be reported when possible. Multiples of the 99th percentile URL should be indicated and reported, both for those with cardiac procedural myocardial injury and those diagnosed with types 4a and 5 MI. Cumulative frequency distribution of peak cTn measurements for MI endpoint assessments by treatment group should also be provided. This will facilitate the comparison of trials and meta-analyses.

38 Silent/unrecognized myocardial infarction in epidemiological studies and quality programmes

ECG monitoring for unrecognized or silent Q wave MI is usually acquired annually in epidemiological studies and clinical trials that assess cardiovascular endpoints. These events are associated with adverse outcomes.¹⁹⁷ There is no firm consensus on how frequently to monitor for ECG evidence of silent Q wave MI or whether surveillance for silent MI events should be routinely implemented. Serial monitoring of patients who have had a symptomatic Q wave MI event revealed Q wave regression in a substantial number of patients.¹⁹⁸ An annual ECG is reasonable in clinical trials to monitor for silent Q wave MI events if the study population is expected to have an accelerated rate of atherosclerotic events. The review should consider the baseline tracing, interim event ECG tracings, and protocol-mandated annual tracings, along with the review of imaging studies if available.

39 Individual and public implications of the myocardial infarction definition

Revision of the definition of MI has a number of implications for individuals, health professionals, and society at large. A tentative or final diagnosis is the basis for advice about further diagnostic testing, lifestyle changes, treatment, and prognosis for the patient. The aggregate of patients with a particular diagnosis is the basis for healthcare planning, and policy and resource allocation.

One of the goals of good clinical practice is to reach a definitive and specific diagnosis, which is supported by current scientific knowledge. The approach to the definition of myocardial injury and MI outlined in this document meets this goal. In general, the conceptual meaning of the term myocardial infarction has not changed, although new sensitive methods have been developed to diagnose this entity. Thus, the diagnosis of an acute MI is a clinical diagnosis based on patient symptoms, ECG changes, and highly sensitive biochemical markers, as well as information gleaned from various imaging techniques.

It should be appreciated that the universal definition of MI may be associated with consequences for patients and their families with

respect to psychological status, life and health insurance, and professional career, as well as driving and pilot licences. The diagnosis is also associated with societal implications with regards to diagnosis-related coding, hospital reimbursement, public health statistics, sick leave, and disability attestation. In order to meet these challenges, physicians must be adequately informed of the diagnostic criteria. Hence, educational materials will need to be created and treatment guidelines must be appropriately adapted.

40 Global perspectives of the definition of myocardial infarction

Cardiovascular disease is a global health problem and prevalence is increasing in the developing world. Understanding the burden and effects of CAD in populations is of critical importance. Changing clinical definitions, criteria, and biomarkers add challenges to our understanding and ability to improve the health of the public. For clinicians, the definition of MI has important and immediate therapeutic implications. For epidemiologists, the data are often retrospective, so consistent case definitions are critical for comparisons and trend analysis. The standards described in this report are suitable for epidemiology studies and for international classification of diseases.¹⁹⁹ However, to analyse trends over time, it is important to have consistent definitions and to quantify adjustments when biomarkers or other diagnostic methods change,²⁰⁰ considering that the advent of cTn has dramatically increased the number of diagnosable MIs for epidemiologists.^{11,201}

In countries with limited economic resources, cardiac biomarkers and imaging techniques may not be available except in a few centres, and even the option of ECG recordings may be lacking. The WHO recommends the use of the ESC/ACC/AHA/WHF Universal Definition of MI in countries without resource constraints, but recommends more flexible standards in resource-constrained locations. Thus, when the only information available is the clinical history and ECG, and when data on cardiac biomarkers are not available or incomplete, the diagnosis of MI can be confirmed by the development of pathological Q waves.¹¹

41 Using the Universal Definition of Myocardial Infarction in the healthcare system

Arriving at a diagnosis of MI using the criteria set forth in this document requires the integration of clinical findings, patterns on the ECG, laboratory data, observations from imaging procedures, and on occasion pathological findings, all viewed in the context of the time horizon over which the suspected event unfolds. Contemporary healthcare systems are increasingly using electronic medical records where medical information is entered, curated, and available for retrieval at a later date. This evolution offers the advantages of a modern electronic database that is useful for a variety of purposes, including scientific discovery and quality improvement in clinical care, but carries with it the challenges of sifting through variable locations and formats where key data elements for confirming a diagnosis of MI

are located. Also, use of the electronic medical record as an epidemiological and research tool of the future is likely to require efforts to verify the accuracy of an acute MI diagnosis, rather than accepting the coded diagnoses used for administrative and billing purposes. Such an effort to create a computable phenotype of MI (further categorized as types 1–5 MI) will require input from informaticians and experts in implementation science to translate the recommendations from this Universal Definition of MI into the routine practice of healthcare delivery and documentation.

Given the evolution of biomarker assays used to support the diagnosis of MI, it is important that a consistent approach be used in the construction of the computable phenotype of MI so as to reliably make comparisons across institutions and track epidemiological trends. Ideally, the information provided should include the assay used to make the diagnosis of MI, the 99th percentile of the URL, and the full sequence of values obtained to discern a rise and fall in biomarker levels.¹⁹⁶

42 Appendix

Approved by the **ESC Committee for Practice Guidelines (CPG)** on behalf of the ESC Board 2016–2018.

ESC National Cardiac Societies actively involved in the review process of the **Fourth Universal Definition of Myocardial Infarction**:

Algeria: Algerian Society of Cardiology, Mohamed Chettibi; **Armenia:** Armenian Cardiologists Association, Hamlet Hayrapetyan; **Austria:** Austrian Society of Cardiology, Franz Xaver Roithinger; **Azerbaijan:** Azerbaijan Society of Cardiology, Farid Aliyev; **Belarus:** Belorussian Scientific Society of Cardiologists, Volha Sujayeva; **Belgium:** Belgian Society of Cardiology, Marc J. Claeys; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Elnur Smajić; **Czech Republic:** Czech Society of Cardiology, Petr Kala; **Denmark:** Danish Society of Cardiology, Kasper Karmak Iversen; **Egypt:** Egyptian Society of Cardiology, Ehab El Hefny; **Estonia:** Estonian Society of Cardiology, Toomas Marandi; **Finland:** Finnish Cardiac Society, Pekka Porela; **The Former Yugoslav Republic of Macedonia:** Macedonian FYR Society of Cardiology, Slobodan Antov; **France:** French Society of Cardiology, Martine Gilard; **Germany:** German Cardiac Society, Stefan Blankenberg; **Greece:** Hellenic Society of Cardiology, Periklis Davlourous; **Iceland:** Icelandic Society of Cardiology, Thorarinn Gudnason; **Israel:** Israel Heart Society, Ronny Alcalai; **Italy:** Italian Federation of Cardiology, Furio Colivicchi; **Kosovo:** Kosovo Society of Cardiology, Shpend Elezi; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Gulmira Baitova; **Latvia:** Latvian Society of Cardiology, Ilja Zake; **Lithuania:** Lithuanian Society of Cardiology, Olivija Gustiene; **Luxembourg:** Luxembourg Society of Cardiology, Jean Beissel; **Malta:** Maltese Cardiac Society, Philip Dingli; **Moldova:** Moldavian Society of Cardiology, Aurel Grosu; **The Netherlands:** Netherlands Society of Cardiology, Peter Damman; **Norway:** Norwegian Society of Cardiology, Vibeke Juliebø; **Poland:** Polish Cardiac Society, Jacek Legutko; **Portugal:** Portuguese Society of Cardiology, João Morais; **Romania:** Romanian Society of Cardiology, Gabriel Tatu-Chitoiu; **Russian Federation:** Russian

Society of Cardiology, Alexey Yakovlev; **San Marino:** San Marino Society of Cardiology, Marco Zavatta; **Serbia:** Cardiology Society of Serbia, Milan Nedeljkovic; **Slovenia:** Slovenian Society of Cardiology, Peter Radsel; **Spain:** Spanish Society of Cardiology, Alessandro Sionis; **Sweden:** Swedish Society of Cardiology, Tomas Jemberg; **Switzerland:** Swiss Society of Cardiology, Christian Müller; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Leila Abid; **Turkey:** Turkish Society of Cardiology, Adnan Abaci; **Ukraine:** Ukrainian Association of Cardiology, Alexandr Parkhomenko; **United Kingdom:** British Cardiovascular Society, Simon Corbett.

Approved by the **ACC Clinical Policy Approval Committee**.

Approved by the **AHA Science Advisory and Coordinating Committee**.

Approved by the **WHF Board**.

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A Proposal for Modest Revision of the Definition of Type 1 and Type 2 Myocardial Infarction

The Universal Definition of Myocardial Infarction (UDMI)¹ classifies myocardial infarction (MI) into 5 subtypes, of which type 1 and type 2 MI are the most common and relevant to practicing clinicians. Type 1 MI is defined as MI caused by acute atherothrombotic mechanisms, with type 2 MI defined as MI resulting from myocardial oxygen supply/demand mismatch without acute atherothrombosis. The UDMI recognizes multiple potential causes of type 2 MI, including demand-side abnormalities such as tachyarrhythmia or severe hypertension, and supply-side issues such as severe anemia, hypoxemia, or hypotension. Type 2 MI may occur with or without obstructive coronary disease, with the threshold for type 2 MI lower in patients with fixed obstructive coronary artery disease.

Type 2 MI is common and is associated with substantial risk for cardiac (and noncardiac) death and major adverse cardiac events.² Research to date has been limited largely to observational studies that have used varying definitions and adjudication criteria for type 2 MI, focusing on prevalence, risk factors, and prognosis, with almost no data on treatment.² Recently, an *International Classification of Diseases, Tenth Revision* (ICD-10) code was introduced for type 2 MI, and it is hoped that this will facilitate research using administrative data.³ However, we believe that the current definition for type 2 MI is too phenotypically heterogeneous to permit adequate study or reliable coding by hospital administrators.

It is important to note that the UDMI includes, under the umbrella of type 2 MI, several acute coronary processes that obstruct blood flow, including spontaneous coronary artery dissection (SCAD), coronary embolism, and coronary vasospasm. We believe that these specific diagnoses are a poor fit in the category of type 2 MI; from both a pathophysiological and clinical perspective, they are more closely aligned with type 1 MI. SCAD, coronary embolism, and vasospasm are acute supply-side obstructive processes that have clinical presentations and initial diagnostic and management approaches that are similar to type 1 MI. They are usually spontaneous presentations, without an obvious precipitating event. These conditions typically are initially triaged as suspected acute coronary syndromes, treated with guideline-recommended therapies for acute coronary syndromes, and evaluated with early coronary imaging. The diagnosis is usually made in the cardiac catheterization laboratory, with subsequent treatment determined by findings from coronary imaging. In contrast, most other etiologies causing type 2 MI, including severe tachycardia and hypertension, anemia, and hypoxemia, are apparent at the time of clinical presentation, and diagnosed based on clinical criteria, with coronary angiography delayed or deferred.

Applying the same diagnosis of type 2 MI to such phenotypically distinct patients has clear disadvantages for clinical management, and negatively impacts the quality of research into type 2 MI. Reporting the epidemiology, outcomes,

James A. de Lemos, MD
L. Kristin Newby, MD,
MHS
Nicholas L. Mills, MD, PhD

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Key Words: anemia ■ coronary artery disease ■ hypertension ■ myocardial infarction ■ tachyarrhythmia

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and treatment responses of type 2 MI, as currently defined, is of little value other than making sure that these diagnoses do not muddy the interpretation of type 1 MI. However, including patients without acute atherothrombosis in the type 1 MI category also creates problems. Clinical trials and guideline recommendations for management of acute coronary syndromes are only applicable to type 1 MI. For example, applying therapies tested in atherothrombosis, such as parenteral anticoagulation and intracoronary stenting, to patients with SCAD may be harmful.⁴ Evidenced-based therapies exist for coronary vasospasm and are emerging for SCAD, with coronary embolism typically managed empirically based on the source of embolism. However, such therapies are clearly distinct from those used to treat acute atherothrombosis.

We propose consideration of a modest redefinition of type 1 and type 2 MI (Figure), with type 1 MI defined by acute coronary obstruction or reduction in coronary blood flow rather than by atherothrombosis. This would move SCAD, coronary embolism, and coronary vasomotor abnormalities (including epicardial vasospasm and microvascular dysfunction) into the type 1 MI category. We further propose subclassifying type 1 MI based on the underlying pathophysiology, with type 1A MI being the typical atherothrombosis category and the other etiologies having separate subclassifications (Figure). Type 2 MI would be defined as MI attributable to acute supply/demand mismatch without acute coronary obstruction. We propose further subclassifying type 2 MI into those with or without obstructive coronary artery disease (Figure), because the subsequent management approaches differ substantially based on

the presence of severe coronary artery disease. As an important corollary, modification of *International Classification of Diseases* (ICD) codes to improve specificity would be an important step forward for research and quality improvement in patients with MI caused by factors other than atherothrombosis.

We believe that this redefinition would better align with modern approaches to diagnosis and management of the spectrum of patients with MI. It would facilitate research into specific diagnostic subcategories and identification of optimal treatment approaches. This designation would also eliminate the need for a separate classification scheme for myocardial infarction with no obstructive coronary disease.⁵ Each of the categories of myocardial infarction with no obstructive coronary disease would fit within the new MI definition construct. Also, the creation of subcategories (type 1A, 1B, etc) would allow room for additional MI phenotypes, as new information on pathophysiology becomes available, without altering the fundamental structure of the classification.

Although some may view differences between the Universal Definition of Myocardial Infarction and our proposed revision as little more than administrative details, we would argue that alignment of diagnosis with clinical presentation, pathophysiology, and diagnostic approach is an essential step to address current knowledge gaps. Moreover, accurate diagnosis has direct implications for quality reporting, because evidence-based standards exist only for MI attributable to atherothrombosis. Clinicians should be held accountable only for adhering to process and performance measures for those patients in whom the measures apply. Finally, and

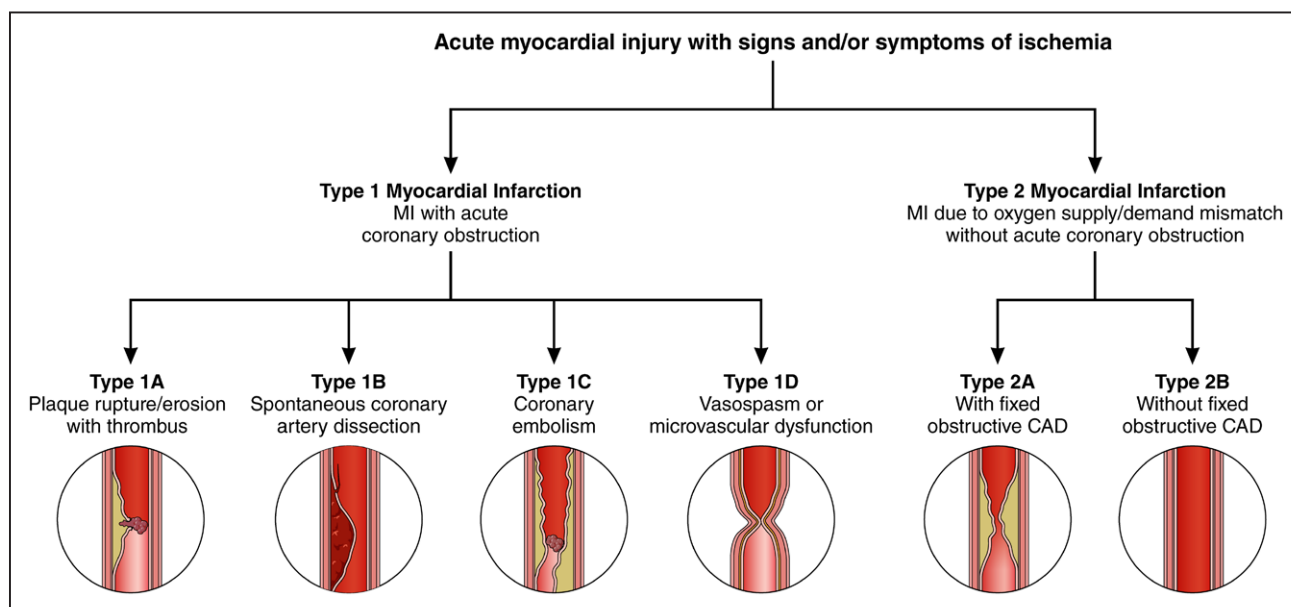


Figure. Proposed revision to Universal Definition of Myocardial Infarction (UDMI).

The proposal redefines type 1 and type 2 MI based on the presence or absence of acute coronary obstruction, with subclassifications based on underlying pathophysiology. This differs from the current UDMI by categorizing spontaneous coronary dissection, coronary embolism, and vasospasm as type 1 MI, and subclassifying type 2 MI based on the presence or absence of fixed obstructive coronary disease. CAD indicates coronary artery disease; and MI, myocardial infarction.

arguably most importantly, as we enter the precision medicine era, it is imperative that our diagnoses be as precise as possible.

ARTICLE INFORMATION

Correspondence

James A. de Lemos, MD, UT Southwestern Medical Center Cardiology, 5909 Harry Hines Blvd, E5.7528, Dallas, TX 75390-8830. Email james.delemos@utsouthwestern.edu

Affiliations

Division of Cardiology, Department of Medicine, University of Texas Southwestern Medical Center, Dallas (J.A.d.L.). Division of Cardiology, Department of Medicine, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC (L.K.N.). British Heart Foundation Centre for Cardiovascular Science and Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, United Kingdom (N.L.M.).

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