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Université Paris Cité

École doctorale Hématologie, Oncogénèse et Biothérapies (ED 561)

Marqueurs cardiovasculaires en situation de stress (UMR-S 942)

Évaluation du couplage auriculo-ventriculaire gauche par imagerie cardiovasculaire multimodale

Par Théo PEZEL

Thèse de doctorat de Biothérapies et Biotechnologies

Dirigée par Patrick HENRY

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Titre de la thèse (français) :

Évaluation du couplage auriculo-ventriculaire gauche par imagerie cardiovasculaire multimodale

Résumé court (français) :

Les maladies cardiovasculaires restent un problème de santé publique majeur, ce qui s'accompagne de coûts directs et indirects extrêmement importants, évalués à plus de 169 milliards d'euros par an au sein de l'Union Européenne, et plus de 350 milliards de dollars par an aux États-Unis. Ainsi, il est absolument crucial de d'élaborer un outil de stratification pronostique précoce capable de détecter les patients les plus à risque de présenter ces événements cardiovasculaires afin de leur offrir une prise en charge personnalisée. Dans ce but, l'imagerie cardiaque multimodale représente un outil non invasif de choix. Alors que de nombreuses études ont montré l'intérêt pronostique de l'évaluation des paramètres structurels et fonctionnels du ventricule gauche et de l'oreillette gauche séparément, aucune étude n'avait jusqu'alors mesuré l'intérêt d'évaluer simultanément le ventricule gauche et l'oreillette gauche. Ainsi, du fait de l'étroite relation physiologique qui existe entre l'oreillette et le ventricule gauches, l'hypothèse de ce travail de thèse de science était que l'évaluation du couplage auriculo-ventriculaire gauche pourrait permettre de refléter l'existence d'une dysfonction auriculo-ventriculaire précoce, et constituer alors un meilleur outil de prédiction précoce du risque d'évènement cardiovasculaire. Pour ce faire, nous avons développé le premier indice de couplage auriculo-ventriculaire gauche décrit dans la littérature à partir d'examen d'IRM cardiaque issus de la cohorte américaine MESA. MESA est étude multicentrique réalisée sur 6 centres américains avec un recrutement prospectif allant de 2000 à 2002, ayant permis de recruter 6 814 participants âgés de 45 à 84 ans. Cet indice de couplage auriculo-ventriculaire gauche (LACI) est défini simplement par le ratio du volume de l'oreillette gauche en télédiastole sur le volume du ventricule gauche en télédiastole. Cet indice exprime alors le pourcentage de dysfonction auriculo-ventriculaire gauche. Une première étude (étude n°1) a montré que le LACI était indépendamment associé à la survenue des événements cardiovasculaires incluant fibrillation atriale, insuffisance cardiaque, et mortalité de cause cardiovasculaire. Afin de pouvoir proposer une utilisation en routine de ce nouvel indice, nous avons déterminé son meilleur seuil de discrimination pronostique qui est de 25%. De plus, le LACI avait une valeur pronostique supérieure à n'importe quel paramètre mesuré de l'oreillette gauche et/ou du ventricule gauches évalués séparément. Dans l'étude n°2, nous avons exploré les déterminants du LACI et de sa variation annuelle sur 10 ans, autrement dit de sa dégradation avec le temps. Dans l'étude n°3, nous avons montré que la ménopause jouait un rôle significatif dans l'accélération de la dégradation de ce couplage auriculoventriculaire gauche impliquant un rôle des hormones sexuels. Dans les études n°4 et 5, nous avons mis en évidence la valeur pronostique de la variation annuelle du LACI sur 10 ans comme un puissant facteur pronostique indépendant de survenue du risque de fibrillation atriale et d'insuffisance cardiaque. Ensuite, nous avons pu valider cette valeur pronostique du LACI sur une cohorte de validation externe française (étude n°6). Enfin, après avoir réalisé les six premiers travaux à partir d'une mesure du LACI par l'IRM cardiaque, nous avons dans l'étude n°7 validé la valeur pronostique du LACI à l'aide de mesures réalisées sur un scanner cardiaque. En effet, la validation de cet indice sur un scanner cardiaque permet d'assurer un développement beaucoup plus large de cette mesure, à travers le monde, compte tenu du fait que le scanner soit largement plus accessible en routine que l'IRM cardiaque. Pour conclure, ce travail de thèse a permis de développer le premier indice de couplage auriculo-ventriculaire

gauche comme marqueur pronostique de risque d'évènements cardiovasculaire à partir d'une cohorte américaine, avec double validation française.

Mots-clés (français) :

Couplage auriculo-ventriculaire gauche, indice de couplage auriculo-ventriculaire gauche (LACI), imagerie par résonance magnétique cardiovasculaire, scanner cardiaque, insuffisance cardiaque, fibrillation auriculaire, pronostic, oreillette gauche, ventricule gauche

Titre de la thèse (anglais) :

Evaluation of the left atrioventricular coupling using multimodality cardiovascular imaging

Résumé court (anglais) :

Cardiovascular diseases remain a major public health problem, which is accompanied by extremely significant direct and indirect costs, estimated at more than 169 billion euros per year within the European Union, and more than 350 billion dollars per year in the United States. Thus, it is absolutely crucial to develop an early prognostic stratification tool capable of detecting patients most at risk of presenting these cardiovascular events to offer them personalized care. For this purpose, multimodality cardiovascular imaging represents a non-invasive tool of choice. While several studies have shown the prognostic interest of evaluating the structural and functional parameters of the left ventricle and the left atrium separately, no study has until now measured the benefit of simultaneously evaluating both the left ventricle and left atrium. Thus, due to the close physiological relationship that exists between the left atrium and the left ventricle, the hypothesis of this work was that the evaluation of the left atrioventricular coupling could make it possible to reflect the existence of early atrioventricular dysfunction, and then constitute a better tool for early prediction of the risk of cardiovascular events. To do this, we developed the first index of left atrioventricular coupling described in the literature based on cardiac MRI examinations from the American MESA cohort. MESA is a multicenter study carried out in 6 American centers with prospective recruitment ranging from 2000 to 2002, having made it possible to recruit 6,814 participants aged 45 to 84 years. This left atrioventricular coupling index (LACI) is defined simply by the ratio of the volume of the left atrium in end-diastole to the volume of the left ventricle in end-diastole. This index then expresses the percentage of left atrioventricular dysfunction. A first study (Study no. 1) showed that LACI was independently associated with the occurrence of cardiovascular events including atrial fibrillation, heart failure, and mortality from cardiovascular causes. To propose routine use of this new index, we have determined its best prognostic discrimination threshold which is 25%. Furthermore, the LACI had a greater prognostic value than any measured parameter of the left atrium and/or left ventricular evaluated separately. In Study no. 2, we explored the determinants of the LACI and its annual variation over 10 years, in other words its deterioration over time. In Study no. 3, we showed that menopause played a significant role in accelerating the degradation of this left atrioventricular coupling implying a role for sex hormones. In Studies no. 4 and 5, we highlighted the prognostic value of the annual variation in LACI over 10 years as a powerful independent prognostic factor for the occurrence of the risk of atrial fibrillation and heart failure. Then, we were able to validate this prognostic value of the LACI on a French external validation cohort (Study no. 6). Finally, after having carried out the first six studies based on a measurement of the LACI by cardiac MRI, in Study no. 7 we validated the prognostic value of the LACI using measurements taken on a cardiac CT. Indeed, the validation of this index on a cardiac CT ensures a much broader development of this measurement, throughout the world, taking into account the fact that the scanner is much more accessible routinely than cardiac MRI. To conclude, this thesis work made it possible to develop the first left atrioventricular coupling index as a prognostic marker of cardiovascular event risk from an American cohort, with double external validation.

Mots-clés (anglais) :

Left Atrioventricular Coupling, Left Atrioventricular Coupling Index (LACI), Cardiovascular Magnetic Resonance, Cardiac CT, Heart failure, Atrial fibrillation, Prognosis, Left atrium, Left ventricle

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Productions scientifiques

Publications dans des revues scientifiques internationales à comité de lecture

Publications sur le travail de thèse (sept publications en premier auteur) :

- **Pezel, T** ; Venkatesh, BA ; De Vasconcellos, HD ; Kato, Y ; Shabani, M ; Xie, E et al , Left Atrioventricular Coupling Index as a Prognostic Marker of Cardiovascular Events: The MESA Study., Hypertension, 2021, 78, 661-671
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- **Pezel, T** ; Ambale-Venkatesh, B ; Quinaglia, T ; Heckbert, SR ; Kato, Y ; de Vasconcellos, HD et al , Change in Left Atrioventricular Coupling Index to Predict Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis (MESA)., Radiology, 2022, 303, 317-326
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- **Pezel T**, Dillinger JG, Toupin S, Mirailles R, Logeart D, Cohen-Solal A, Unger A, Canuti ES, Beauvais F, Lafont A, Gonçalves T, Lequipar A, Gall E, Boutigny A, Ah-Sing T, Hamzi L, Lima JAC, Bousson V, Henry P. Left atrioventricular coupling index assessed using cardiac CT as a prognostic marker of cardiovascular death. *Diagn Interv Imaging.* 2023:S2211-5684(23)00146-8.
- **Pezel T**, Garot P, Toupin S, Sanguineti F, Hovasse T, Untersee T, Champagne S, Morisset S, Chitiboi T, Jacob AJ, Sharma P, Venkatesh BA, Lima JAC, Garot J. AI-Based Fully Automated Left Atrioventricular Coupling Index as a Prognostic Marker in Patients Undergoing Stress CMR. *JACC Cardiovasc Imaging.* 2023:S1936-878X(23)00112-2.

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- **Pezel, T** ; Viallon, M ; Croisille, P ; Sebbag, L ; Bochaton, T ; Garot, J et al, Imaging Interstitial Fibrosis, LV Remodeling, and Function in Stage A and B Heart Failure., *JACC Cardiovasc Imaging*, 2021, 14, 1038-1052

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- **Pezel T**, Untersee T, Hovasse T, Sanguineti F, Garot P, Champagne S, Toupin S, Ah-Sing T, Faradji A, Nicol M, Hamzi L, Dillinger JG, Henry P, Bousson V, Garot J. Safety and incremental prognostic value of stress cardiovascular magnetic resonance in patients with known chronic kidney disease. *J Cardiovasc Magn Reson.* 2023;25(1):29.
- **Pezel T**, Garot P, Toupin S, Hovasse T, Sanguineti F, Champagne S, Morisset S, Chitiboi T, Jacob AJ, Sharma P, Untersee T, Garot J. Prognostic impact of artificial intelligence-based fully automated global circumferential strain in patients undergoing stress CMR. *Eur Heart J Cardiovasc Imaging.* 2023; jead100.
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- Dillinger, JG ; Achkouty, G ; Albert, F ; Muller, G ; Labèque, JN ; Moisson, L ; **Pezel, T** et al , Deleterious synergistic effects of acute heart failure and diabetes mellitus in patients with acute coronary syndrome: Data from the FAST-MI Registries., *Arch Cardiovasc Dis*, 2022, 115, 264-275
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Partie 1 :

Introduction générale

1-A) Enjeux de santé publique de l'insuffisance cardiaque et de la fibrillation auriculaire

Enjeux de l'Insuffisance cardiaque

L'insuffisance cardiaque est une condition caractérisée par une incapacité du cœur à pomper suffisamment de sang pour répondre aux besoins du corps (1,2). Elle est l'une des principales causes de mortalité dans le monde et un problème majeur de santé publique (3), en particulier chez les personnes âgées. La prévalence de l'insuffisance cardiaque est d'environ 1 à 2 % de la population adulte dans les pays développés, atteignant ≥ 10 % chez les personnes de plus de 70 ans (2,4,5). Les principales causes de l'insuffisance cardiaque comprennent l'hypertension artérielle, les maladies coronaires, les malformations cardiaques congénitales, les infections virales et les troubles du rythme cardiaque (2). Le dépistage précoce de l'insuffisance cardiaque repose sur l'évaluation des symptômes tels que l'asthénie, la dyspnée, l'apparition d'œdème et la diminution de la capacité d'effort (2,4). Des tests diagnostiques, tels que l'échocardiographie et l'électrocardiogramme (ECG), sont essentiels pour confirmer le diagnostic (2). La prévention de l'insuffisance cardiaque implique la gestion des facteurs de risque cardiovasculaires modifiables, tels que le tabagisme, l'obésité, le diabète et l'inactivité physique (4,6–9). Un traitement précoce et une prise en charge multidisciplinaire sont nécessaires pour réduire les complications et améliorer la qualité de vie des patients atteints d'insuffisance cardiaque (6).

Enjeux de la Fibrillation atriale

La fibrillation atriale est un trouble du rythme cardiaque caractérisé par une contraction irrégulière et rapide des oreillettes (6,10). Cette pathologie augmente considérablement le risque d'accident vasculaire cérébral et d'insuffisance cardiaque (1,3). Le dépistage de la fibrillation atriale repose sur l'évaluation des symptômes tels que les palpitations, la dyspnée et l'asthénie. Le diagnostic repose sur la réalisation d'un ECG douze dérivations ou d'un Holter-ECG. La prévention de la fibrillation atriale implique une gestion adéquate des facteurs de risque, tels que l'hypertension artérielle, le diabète, l'obésité et l'alcool (6,11). Des mesures de prévention supplémentaires comprennent l'utilisation d'anticoagulants pour réduire le risque d'accident vasculaire cérébral chez les patients atteints de fibrillation atriale à haut risque (2,12,13). Des traitements visant à contrôler le rythme cardiaque et à prévenir les complications associées, tels que l'ablation par cathéter peuvent être nécessaires dans certains cas (2).

Les enjeux de santé publique liés à l'insuffisance cardiaque et la fibrillation atriale sont considérables, compte tenu de leur prévalence croissante (1,14,15) et de leurs conséquences graves sur la santé des individus. Le dépistage précoce et la prévention jouent un rôle crucial dans la gestion de ces conditions. Il est essentiel d'encourager la sensibilisation du public aux facteurs de risque cardiovasculaires modifiables, de promouvoir un mode de vie sain et d'améliorer l'accès aux soins de santé pour assurer un dépistage précoce et une prise en charge adéquate. La collaboration entre les professionnels de la santé, les chercheurs et les décideurs politiques est nécessaire pour relever ces défis et réduire l'impact de ces pathologies sur la santé publique.

1-B) Besoin d'outils de stratification pronostique précoce en prévention primaire

Prévention primaire et rôle des outils de dépistage

La prévention primaire en cardiologie désigne l'ensemble des interventions mises en place pour empêcher l'apparition de maladies cardiovasculaires chez des individus à risque (16). L'identification précoce de ces individus s'avère cruciale pour instaurer un suivi et une prise en charge adaptés, afin de prévenir les événements cardiaques. Les outils de dépistage jouent à cet égard un rôle essentiel, permettant une stratification précise du risque individuel de développer une insuffisance cardiaque ou une fibrillation atriale (2,6,17).

Outils de dépistage de l'insuffisance cardiaque

Parmi les outils de stratification pronostique actuels pour l'insuffisance cardiaque, on trouve le score de Framingham, qui combine plusieurs facteurs de risque tels que l'âge, le sexe, la pression artérielle systolique, le diabète, la présence d'un souffle cardiaque, l'indice de masse corporelle, et le traitement par des médicaments pour l'hypertension (18,19). D'autres modèles de prédiction incluent le Health ABC Heart Failure Model (20), basé sur des paramètres cliniques simples et des biomarqueurs tels que la cystatine C et le NT-proBNP. L'imagerie cardiaque, telle que l'échocardiographie, joue également un rôle clé dans l'évaluation du risque d'insuffisance cardiaque (21), en permettant d'évaluer la fonction ventriculaire gauche et la présence de maladies valvulaires (22).

Outils de dépistage de la fibrillation atriale

Pour la fibrillation atriale, les outils de dépistage actuels comprennent l'ECG standard et l'Holter-ECG, qui permettent d'identifier les anomalies du rythme cardiaque. Plus récemment, l'émergence des montres connectées (23) et des appareils portables a ouvert de nouvelles perspectives pour la détection précoce de la fibrillation atriale (24). Ces dispositifs

peuvent enregistrer l'ECG en continu et détecter les irrégularités du rythme cardiaque, facilitant ainsi le dépistage des cas asymptomatiques (25). En outre, des scores de risque tels que le score CHARGE-AF (*Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation*) ont été développés pour prédire le risque de fibrillation atriale puis d'AVC chez les patients en FA (26), en tenant compte des facteurs de risque tels que l'âge, le sexe, l'hypertension, le diabète, et l'insuffisance cardiaque. Le rôle des facteurs métaboliques dans la survenue de la fibrillation atriale est également de plus en plus reconnu (6,11,27,28), soulignant l'importance d'une approche globale de la prévention incluant le contrôle du poids, de la glycémie et du cholestérol.

La stratification pronostique précoce en prévention primaire est essentielle pour identifier les patients à risque d'insuffisance cardiaque et de fibrillation atriale. Les outils de dépistage disponibles permettent d'évaluer de manière précise et détaillée le risque individuel, en prenant en compte des facteurs de risque spécifiques à chaque pathologie. La mise en place d'une prise en charge et d'un suivi personnalisé pour les patients identifiés à risque revêt une importance capitale. En effet, ces individus pourront bénéficier d'interventions préventives telles que des modifications du mode de vie, des traitements médicamenteux appropriés, voire des interventions chirurgicales si nécessaire. Une détection précoce permettra également de surveiller de près l'évolution de leur état de santé et d'adapter les interventions en conséquence. Il est donc crucial de promouvoir l'utilisation de ces outils de stratification pronostic précoce en prévention primaire afin d'identifier les individus à risque d'insuffisance cardiaque et de fibrillation atriale. Cela permettra de mieux cibler les ressources médicales et de mettre en place des mesures préventives adéquates pour réduire les complications cardiovasculaires et améliorer la qualité de vie des patients.

1-C) Place de l'imagerie cardio-vasculaire multimodale dans la stratification pronostique précoce du risque d'insuffisance cardiaque et de fibrillation atriale

L'imagerie cardio-vasculaire multimodale, comprenant l'échographie cardiaque, l'I.R.M. cardiaque et le scanner cardiaque, joue un rôle essentiel dans la stratification pronostique précoce des patients à risque d'insuffisance cardiaque et de fibrillation atriale. Chacun de ces examens d'imagerie offre des informations spécifiques et complémentaires, permettant une évaluation précise du risque individuel et facilitant la mise en place de mesures préventives adaptées.

Place de l'échographie cardiaque

L'échographie cardiaque est un outil de dépistage couramment utilisé pour évaluer la structure et la fonction cardiaque. Elle permet de détecter précocement des anomalies structurelles et fonctionnelles, ainsi que des signes précurseurs de l'insuffisance cardiaque et de la fibrillation atriale. Parmi les paramètres utilisés pour la stratification pronostic précoce, on retrouve l'évaluation de la fraction d'éjection ventriculaire gauche, la mesure des volumes cardiaques (ventricules et oreillettes), l'analyse des flux sanguins et l'évaluation des biomarqueurs spécifiques.

Rôle de l'I.R.M. cardiaque

L'I.R.M. cardiaque offre une visualisation détaillée de l'anatomie et de la fonction cardiaque, en fournissant des images de haute résolution (29,30). Elle permet une évaluation précise de la fibrose myocardique (7), de l'ischémie myocardique (31–33) et de la présence de tissu cicatriciel (34,35), qui sont des facteurs de risque reconnus pour le développement de l'insuffisance cardiaque et de la fibrillation atriale (7). L'utilisation de paramètres tels que le

volume de fibrose, la cinétique ventriculaire, le flux sanguin myocardique et l'évaluation de la viabilité myocardique permettent une stratification pronostic précoce des patients symptomatiques (36–41) et asymptomatiques (42–44) à risque.

Intérêt du scanner cardiaque

Le scanner cardiaque offre une évaluation non invasive de l'anatomie coronaire, permettant de détecter précocement une sténose coronaire significative (45–47). Cette information est essentielle dans la stratification pronostic précoce des patients, car l'obstruction coronaire est un facteur de risque majeur pour le développement de l'insuffisance cardiaque et de la fibrillation atriale (46,48,49). De plus, le scanner cardiaque permet d'évaluer la calcification coronaire (50–52), qui est un marqueur de l'athérosclérose et un prédicteur de risque cardio-vasculaire (39,53,54).

L'imagerie cardio-vasculaire multimodale, comprenant l'échographie cardiaque, l'I.R.M. cardiaque et le scanner cardiaque, offre une approche complète et précise dans la stratification pronostique précoce des patients à risque d'insuffisance cardiaque et de fibrillation atriale en prévention primaire. Chacun de ces examens d'imagerie fournit des informations spécifiques et complémentaires, permettant une évaluation précise du risque individuel. L'utilisation de ces outils aide à une prise en charge personnalisée et adaptée, visant à prévenir les complications cardio-vasculaires et à améliorer la qualité de vie des patients. L'imagerie cardio-vasculaire multimodale représente ainsi un enjeu majeur pour la gestion des patients en prévention primaire des événements cardio-vasculaires.

1-D) Intérêt pronostique de l'évaluation morphologique et fonctionnelle de l'oreillette gauche et du ventricule gauche évalués séparément par imagerie

Dans la prédiction du risque d'événements cardiovasculaires, le rôle du VG est établi depuis longtemps, dans la population générale et notamment chez les insuffisants cardiaques (7,55). Les dimensions du VG et la fonction systolique, cette dernière principalement exprimée en fraction d'éjection (FEVG), ont été les premières variables étudiées. Au fil des ans, le rôle des prédicteurs des résultats cardiovasculaires s'est étendu à une augmentation de la masse du VG (c'est-à-dire une hypertrophie) et à une géométrie altérée de la chambre (56,57), à une augmentation de la rigidité et à une réduction des propriétés de remplissage (dysfonctionnement diastolique) et, plus récemment, à des altérations infracliniques de la fonction systolique (effort myocardique et taux d'effort), dans le but d'identifier des facteurs prédictifs de risque à un stade précoce du dysfonctionnement, lorsque la fraction d'éjection peut encore être normale(22,58).

Au cours des 2 dernières décennies, l'oreillette gauche (OG) a été identifiée comme un biomarqueur important pour stratifier le risque d'évènements cardiovasculaires (59,60). L'OG est connue pour se dilater en réponse à la maladie de la valve mitrale, à l'hypertension artérielle, à l'augmentation de la masse du VG et, en général, à toute condition qui augmente les pressions de remplissage du VG (61,62). Ainsi, la taille de l'OG peut être considérée comme un indicateur indirect des pressions de remplissage du VG. De plus, l'élargissement de l'OG a été associé à un risque accru de décès (63), d'accident vasculaire cérébral (64), d'insuffisance cardiaque (65,66), et de développement de la fibrillation auriculaire (62,67,68).

L'évaluation de la taille de l'OG a été initialement réalisée en utilisant le diamètre antéro-postérieur, tel que mesuré par échocardiographie transthoracique en fin de systole, lorsque la dimension de l'oreillette est la plus grande. Bien que facile à mesurer, reproductible et donc adapté à la fois à des fins cliniques et à de grandes études de population, le diamètre de l'OG

est un mauvais indicateur du volume réel de l'OG, qui est connu pour s'agrandir de manière asymétrique en réponse à divers stimuli. L'évaluation du volume de l'OG par échocardiogramme bidimensionnel représentait donc une amélioration substantielle de l'évaluation de la taille de l'OG et du risque d'événements associé, permettant des mesures plus précises et moins chargées d'hypothèses géométriques. Plus récemment, l'introduction de l'échocardiographie tridimensionnelle a permis l'évaluation du volume OG en temps réel tout au long du cycle cardiaque et, par conséquent, une mesure précise des volumes auriculaires maximum et minimum et l'analyse des paramètres fonctionnels, tels que la fraction de vidange de l'OG (fraction d'éjection de l'OG, FEOG) (69,70).

1-E) L'hypothèse du couplage auriculo-ventriculaire gauche (OG/VG)

La taille et la fonction de l'oreillette gauche (OG) ont été popularisées en tant que baromètres de la pression de remplissage ventriculaire gauche (VG) et de la fonction diastolique. Cependant, le rôle spécifique de l'OG, indépendante du VG, et son évaluation clinique restent difficiles. Plusieurs études récentes ont suggéré que la mesure des changements de volume OG (59,69), de la déformation de la paroi atriale (68,71) ou de l'étendue de la fibrose de la paroi atriale (72) peut être cliniquement utile pour prédire les événements cardiaques indésirables tels que la fibrillation auriculaire et la mortalité chez les patients avec un dysfonctionnement diastolique du VG.

La fonction atriale gauche montre des variations phasiques au cours des différentes périodes du cycle cardiaque (59). L'oreillette gauche fonctionne comme une chambre de réception et de dilatation (réservoir) pendant la systole ventriculaire, permettant à un flux ininterrompu

d'arriver dans l'oreillette même lorsque la valve mitrale est fermée. Le flux provenant des veines pulmonaires gauches pénètre dans la cavité atriale gauche et commence à tourner le long d'un axe en forme de croissant parallèlement à la ligne de fermeture en forme de C des feuillets de la valve mitrale (73). En revanche, le flux provenant des veines pulmonaires droites se déplace séparément le long de la paroi atriale gauche, créant des flux sanguins sans collision. Ces flux sanguins lavent la surface atriale gauche, évitant la stase hémodynamique et la formation de thrombus, tandis que le réservoir atrial gauche se dilate pour atteindre son volume maximal. On pourrait supposer que l'absence d'une chambre auriculaire intermédiaire arrêterait le mouvement vers l'avant du flux sanguin veineux lorsque la valve mitrale est fermée et laisserait l'énergie cinétique du sang en mouvement se convertir en une poussée de pression statique qui pourrait endommager l'architecture veineuse pulmonaire pendant chaque systole ventriculaire. Cette action de protection des oreillettes en dilatation qui maintient un flux sanguin continu vers l'avant dans la systole reste largement sous-estimée.

Les phases de remplissage diastolique montrent des interactions hémodynamiques plus complexes (59). Au début de la diastole, la rotation du flux sanguin cesse dans l'oreillette gauche lorsque le sang tombe dans la cavité ventriculaire gauche (remplissage passif) mais contribue à la formation d'un vortex à l'intérieur de la cavité ventriculaire gauche (74). Ce vortex diastolique précoce dans la cavité ventriculaire gauche est plus fort que la rotation du flux observée dans l'OG et assure une accumulation d'énergie cinétique qui est utilisée pour élargir le ventricule gauche à un volume télé-diastolique plus élevé (74). Étant donné que l'expansion du VG dépasse largement la décompression volumique de l'oreillette gauche, un grand volume de sang est directement aspiré dans le ventricule gauche à partir de la circulation veineuse pulmonaire (volume du conduit). Pendant la période de diastasis, la vitesse du flux transmitral est transitoirement réduite avant le début de la contraction auriculaire (remplissage

actif ou booster), ce qui dynamise le flux à la fin de la diastole ventriculaire et de la formation de vortex. Le vortex de flux dans la diastole tardive aide à rediriger le flux atrial gauche vers la région de sortie VG et a été suggéré pour aider à amorcer le VG pendant la pré-éjection, étirant les cardiomyocytes durant la pré-charge avec des contraintes de raccourcissement du VG selon la loi de Frank-Starling (75).

La présence d'une hypertrophie ventriculaire gauche et d'un dysfonctionnement diastolique, comme on le voit chez les patients souffrant d'hypertension artérielle, est associée à une perte d'aspiration diastolique précoce et à une diminution de la compliance. L'augmentation des pressions de remplissage du VG empêche la décompression de l'OG au début de la diastole. L'OG s'adapte en augmentant le volume actif de vidange atriale gauche. De plus, l'élévation chronique des pressions de remplissage crée plus de contraintes sur les parois, ce qui dilate la cavité atriale gauche, augmentant les volumes minimal et maximal de l'OG ; il a été rapporté qu'une augmentation du volume minimal atrial gauche reflète davantage l'élévation des pressions de remplissage du VG. L'augmentation du volume atrial gauche augmente encore le stress de la paroi et déclenche l'hypertrophie et la fibrose des myocytes. De plus en plus de preuves, issues d'études cliniques et expérimentales, suggèrent que les patients atteints de dysfonction diastolique présentent un remodelage fibrotique simultané de l'OG et du VG (71,76). On peut s'attendre à ce que la présence de fibrose du tissu auriculaire modifie la forme de l'OG et les propriétés des tissus. En effet, les patients atteints de fibrillation atriale paroxystique ou persistante perdent la capacité de distendre l'OG, entraînant une perte de fonction de réservoir; une réduction de la fonction de réservoir atrial gauche est un prédicteur indépendant de la survenue d'une arythmie auriculaire (59,67).

Le couplage auriculo-ventriculaire gauche est un processus dynamique et variable dans le temps. La perte fondamentale de la fonction du réservoir atrial gauche, telle que celle évaluée par le strain en échocardiographie ou IRM cardiaque, identifie un stade avancé de remodelage atrial gauche par rapport à la taille de l'OG seule et est étroitement associée à des événements cliniques indésirables, notamment la fibrillation atriale, une insuffisance cardiaque et la mort (68,77). Ce stade peut probablement être caractérisé morphologiquement par la présence d'une fibrose du VG vérifiée par IRM cardiaque (7). Les données des deux techniques fournissent des informations mécanistes sur la même échelle évolutive et doivent être comparées pour construire un algorithme précis et rentable.

Ainsi, l'objectif de ce travail de thèse de science est d'élaborer le premier indice de couplage auriculo-ventriculaire gauche décrit dans la littérature, d'en étudier les déterminants et mécanismes impliqués, puis de le valider comme marqueur pronostique indépendant du risque de survenue d'évènements cardiovasculaires. Afin d'adresser cet objectif, l'IRM cardiaque représente un outil non invasif de choix car il est l'examen de référence le plus robuste pour l'évaluation des paramètres morphologiques du VG et de l'OG (29,30). Alors que de nombreuses études ont montré l'intérêt pronostique de l'évaluation des paramètres structurels et fonctionnels du ventricule gauche (55,56,78,79) et de l'oreillette gauche séparément (80), aucune étude n'a jusqu'à présent mesuré l'intérêt d'évaluer simultanément le VG et l'OG. Ainsi, du fait de l'étroite relation physiologique qui existe entre l'OG et le VG, rapportée par plusieurs études (81–83), l'hypothèse de ce travail de thèse de science est que l'évaluation du couplage auriculo-ventriculaire gauche permettrait de refléter l'existence d'une dysfonction auriculo-ventriculaire précoce, et constituerait alors un meilleur outil de prédiction précoce du risque d'évènements cardiovasculaires.

Partie 2 :

Étude n°1 : Développement du premier index de couplage auriculo-ventriculaire gauche par IRM cardiaque

Left Atrioventricular Coupling Index as a Prognostic Marker of Cardiovascular Events: The MESA Study

Pezel, T ; Venkatesh, BA ; De Vasconcellos, HD ; Kato, Y ; Shabani, M ; Xie, E et al.
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Les paramètres fonctionnels de l'oreillette gauche et du ventricule gauche influencent le pronostic des patients atteints de maladies cardiovasculaires. Cette première étude du travail de thèse visait à étudier la valeur pronostique d'un nouvel indice de couplage auriculo-ventriculaire gauche (LACI – *left atrio-ventricular coupling index*) dans une population sans antécédents de maladies cardiovasculaires au départ issus de la cohorte MESA (*Multi-Ethnic Study of Atherosclerosis* – étude multiethnique sur l'athérosclérose). Les participants à MESA qui ont subi une évaluation initiale par IRM cardiovasculaire ont été analysés. Le LACI était défini par le rapport du volume télédiastolique auriculaire gauche divisé par le volume télédiastolique ventriculaire gauche. Des modèles de risque proportionnel de Cox ont été utilisés pour évaluer l'association entre le LACI et la fibrillation auriculaire, l'insuffisance cardiaque, le décès de cause coronaire et les maladies cardiovasculaires graves définies par un infarctus du myocarde, un arrêt cardiaque récupéré, un accident vasculaire cérébral ou un décès de cause coronaire. Parmi les 4124 participants (62±10 ans, 47% d'hommes), 1074 événements cardiovasculaires ont été observés avec un suivi moyen de 13±3 ans. Une valeur

de LACI élevée était indépendamment associée à la fibrillation auriculaire (*hazard ratio* – HR, 1,86 [IC à 95 %, 1,69-2,04]), à l’insuffisance cardiaque (HR, 1,50 [IC à 95 %, 1,38-1,62]), aux maladies cardiovasculaires graves (HR 1,23 [IC à 95 %, IC, 1,13–1,34]) et aux décès de cause coronaire (HR 1,29 [IC à 95 %, 1,15–1,45] ; tous les $p < 0,0001$). Après ajustement sur les facteurs de risque cardiovasculaire traditionnels, le LACI a montré une amélioration significative de la discrimination et de la reclassification des modèles par rapport aux modèles standard actuellement utilisés pour prédire le risque d’insuffisance cardiaque ou de fibrillation atriale. Ainsi, cette première étude montre que le LACI est un bon prédicteur de l’incidence de l’insuffisance cardiaque, de la fibrillation auriculaire, des maladies cardiovasculaires graves et des décès de cause coronaire. Le LACI a une valeur pronostique additionnelle pour prédire les événements cardiovasculaires par rapport aux facteurs de risque traditionnels et un meilleur pouvoir de discrimination et de reclassification par rapport aux paramètres individuels de l’oreillette gauche ou du ventricule gauche évalués séparément.

En résumé, cette première étude permet de définir pour la première fois un index de couplage auriculo-ventriculaire gauche que nous avons décrit pour la première fois avec l’équipe du Professeur Joao Lima au sein du *Johns Hopkins Hospital* (Baltimore, USA), lors de la mobilité recherche de deux ans du doctorant. Avec ce premier travail, nous démontrons la valeur prédictive d’un nouvel indice de couplage auriculo-ventriculaire gauche, le LACI, pour la fibrillation auriculaire, l’insuffisance cardiaque, et les maladies cardiovasculaires graves dans une population multiethnique (MESA), âgée de 45 à 84 ans, sans maladie cardiovasculaire clinique au moment de l’inclusion. À notre connaissance, cette étude est la première à décrire l’utilisation d’un couplage auriculo-ventriculaire gauche comme outil de stratification pronostique avec une valeur pronostique incrémentale au-delà des facteurs de risque cliniques traditionnels.

ORIGINAL ARTICLE

Left Atrioventricular Coupling Index as a Prognostic Marker of Cardiovascular Events: The MESA Study

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ABSTRACT: Both left atrial and left ventricular functional parameters influence the prognosis of patients with cardiovascular diseases. This study aimed to investigate the prognostic value of a novel left atrioventricular coupling index (LACI) in a population without history of cardiovascular diseases at baseline. Participants of the Multi-Ethnic Study of Atherosclerosis who underwent a baseline cardiovascular magnetic resonance study were analyzed. LACI was defined by the ratio of the left atrial end-diastolic volume divided by the left ventricular end-diastolic volume. Cox proportional hazard models were used to evaluate the association between LACI and atrial fibrillation, heart failure, coronary heart disease death, and hard cardiovascular disease defined by myocardial infarction, resuscitated cardiac arrest, fatal and nonfatal stroke, or coronary heart disease death. Among the 4124 participants (61.5±10.1 years, 47.4% men), 1074 cardiovascular events were observed (mean follow-up, 13.0±3.2 years). Greater LACI was independently associated with atrial fibrillation (hazard ratio, 1.86 [95% CI, 1.69–2.04]), heart failure (hazard ratio, 1.50 [95% CI, 1.38–1.62]), hard cardiovascular disease (1.23 [95% CI, 1.13–1.34]), and coronary heart disease death (hazard ratio, 1.29 [95% CI, 1.15–1.45]; all $P < 0.0001$). After adjustment for traditional cardiovascular risk factors, LACI showed significant improvement in model discrimination and reclassification compared with currently used standard models to predict outcomes. LACI is a strong predictor for the incidence of heart failure, atrial fibrillation, hard cardiovascular disease, and coronary heart disease death. LACI has incremental prognostic value to predict cardiovascular events over traditional risk factors and better discrimination and reclassification power compared with individual left atrial or left ventricular parameters. (*Hypertension*. 2021;78:00–00. DOI: 10.1161/HYPERTENSIONAHA.121.17339.)

• [Data Supplement](#)

Key Words: atrial fibrillation ■ heart failure ■ myocardial infarction ■ prognosis ■ risk factors

Cardiovascular diseases (CVD) remain a major public health problem affecting 24.3 million people in the United States, with estimated direct and indirect costs of 351.2 billion dollars in 2015.¹ Several left ventricular (LV) structural and functional parameters, such as LV ejection fraction (LVEF), LV myocardial strain, LV mass to volume ratio, or LV global function index, have shown prognostic value in predicting the occurrence of CVD.^{2–5} However, many studies emphasize the fact that CVD does not occur exclusively because of impaired LV structure and function.⁶ Even with preserved LV systolic

function, left atrial (LA) dysfunction may impair global heart performance and uncoupling between functional performance of the 2 chambers can also contribute to cardiac dysfunction and clinical heart disease.⁷

Atrioventricular coupling is complex because chamber filling, emptying, and active contraction are not synchronous. The atria fill as the ventricles contract and eject blood into the pulmonary and systemic circulations. They empty as the ventricles relax, but, in sinus rhythm, contract at the end of ventricular diastole. Here, we time simultaneous atrioventricular function in reference to ventricular

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Novelty and Significance

What Is New?

- Using cardiovascular magnetic resonance data, a new left atrioventricular coupling index was identified in a large cohort of patients without cardiovascular disease at enrollment: the MESA (Multi-Ethnic Study of Atherosclerosis).
- This index was independently associated with the occurrence of cardiovascular events, showing an incremental long-term prognostic value over and above traditional clinical risk factors.

What Is Relevant?

- The concept of left atrioventricular coupling is support by this coupling index which has a better prognostic

value than individual left atrium or left ventricle parameters measured separately.

- This left atrioventricular index could be also assessed using echocardiography allowing its worldwide spread even more easily.

Summary

The simple method to measure this new left atrioventricular index allows rapid and immediate clinical routine use as a cardiovascular risk stratification tool. Given that the assessment of the left atrioventricular coupling has shown a more powerful and earlier stratification of cardiovascular risk than individual left atrium or left ventricle parameters measured separately, further work should study this coupling more precisely.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CHD	coronary heart disease
CMR	cardiovascular magnetic resonance
CVD	cardiovascular disease
HF	heart failure
HR	hazard ratio
IDI	integrative discrimination index
LA	left atrium
LACI	left atrioventricular coupling index
LV	left ventricle
LVEF	left ventricular ejection fraction
MESA	Multi-Ethnic Study of Atherosclerosis
NRI	net reclassification improvement
NT-proBNP	N-terminal pro-B-type natriuretic peptide

systole and diastole. Indeed, deterioration in LA structure, described as a higher end-systolic LA volume index, is an independent marker of heart failure (HF).^{8,9} Moreover, LA end-diastolic volume index is strongly associated with CVD.^{10,11} LA end-diastolic volume has been reported as a better predictor of survival compared with LA end-systolic volume, given a better sensitivity for elevated LV filling pressure.^{10,11} Consequently, the concept of atrial failure has been proposed, based on the principle that even in the absence of LV disease, atrial fibrotic changes and dysfunction may trigger HF or atrial fibrillation (AF).¹² Recently, LA maximum longitudinal end-systolic strain was suggested as superior to LA end-systolic volume as an index cardiac diastolic dysfunction,¹³ and in association with HF, AF, and death.¹⁴

Although LA and LV parameters have independent prognostic value, the close physiological relationship between LA and LV^{15,16} suggest that the assessment of LA/LV coupling could better reflect left atrioventricular dysfunction and be a better predictor of CVD. A single left atrioventricular parameter measuring simultaneously LA and LV could be very useful in clinical routine to improve the early prediction of CV outcomes. Indeed, LA and LV are directly connected during diastole and, in the absence of valvular heart disease, their function and filling pressures are tightly coupled.^{17,18} However, very few studies have ever investigated a LA/LV coupling index with very limited sample sizes.^{19,20} Based on such rationale, we designed an analysis to examine the association of atrioventricular coupling parameters with incident CVD in a prospective population study of individuals without history of previous heart disease. In this study, therefore, we aim to investigate the prognostic value of a new left atrioventricular coupling index (LACI), defined by the ratio between the LA end-diastolic volume and the LV end-diastolic volume assessed by cardiovascular magnetic resonance imaging (CMR), to predict the occurrence of cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The MESA study is a prospective, population-based multi-ethnic (White, Black, Chinese, and Hispanic) cohort study of sub-clinical CVD. The study design of MESA has been described in detail previously.²¹ In summary, between 2000 and 2002 (exam 1), 6814 men and women aged from 45 to 84 years,

free of clinical CVD at enrollment, were recruited from 6 US field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN). The methodology of baseline characteristics collection is detailed in Text 1 in the [Data Supplement](#). Blood pressure was measured 3× using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon; Tampa, FL) while the participants were resting in a seated position. The average of the last 2 measurements were used in the analysis. Participants with significant valvular disease at baseline were excluded. All participants provided written informed consent. All study protocols were approved by the institutional review boards of each participating field center.

A flowchart of the MESA population investigated in this study is depicted in Figure 1.

Of the 4285 participants with baseline CMR study including LA volume assessment (exam 1), 21 individuals had no follow-up for cardiovascular events, 77 participants had missing images or a not sufficient image quality to measure LA and LV volumes, and another 63 had missing covariates, resulting in a final cohort of 4124 subjects available for the analysis of this proposed study (Figure 1).

CMR Protocol and Image Analysis

At baseline, CMR was performed with 1.5 T MR scanners: Signa LX or CVi (GE Medical Systems, Waukesha, WI) or Symphony or Sonata (Siemens Medical Systems, Erlangen, Germany). Long-axis cine images were obtained from 2-chamber and 4-chamber views, using ECG-gated fast gradient-echo pulse sequences. A stack of short-axis cine images was acquired to encompass both ventricles and LV end-diastolic volume was measured using cardiac image modeler software (CIM version 6.0, University of Auckland, New Zealand). All cine images were acquired with a temporal resolution of ≈50 ms. The complete CMR protocol, as well as details on image analysis, data quality control, calculations for LVEF, LV mass and volumes, LA volumes, and reproducibility of these measurements have been published previously.²²

Multimodality tissue-tracking software (MTT version 6.0, Toshiba Medical Systems Corporation, Tokyo, Japan) was used to quantify LA volume and strain from 2- and 4- chamber cine CMR images (Text 2 in the [Data Supplement](#)). This method has been validated previously with good to excellent intra- and inter-reader reproducibility with intraclass correlation of 0.88 to

0.98 ($P<0.001$), and pretty good interstudy reproducibility with intraclass correlation of 0.44 to 0.82 ($P<0.05$ to 0.001).^{23–25} A single experienced operator blinded to the case status of the participant defined endocardial and epicardial borders of the LA at end-systole. Using the marked points, the software creates endocardial and epicardial borders, then tracks LA tissue in subsequent frames. The endocardial and epicardial contours generated by the software are then followed by the operator during the cardiac cycle for quality control.

Left Atrioventricular Coupling Index

LACI was defined for each participant by the ratio between the LA end-diastolic volume and the LV end-diastolic volume assessed by CMR. The LV volume was measured from the stack of short-axis cine images, while the LA volume was measured from the 2-chamber and 4-chamber views, as previously described. The LA and LV volumes were measured with a match in the same end-diastolic phase defined by the mitral valve closure (Figure 2). In addition, LACI measured in end-diastole was more accurate to predict outcomes than the assessment of a left atrioventricular coupling index performed in end-systole (Table S1). The intra- and inter-reader reproducibility of the LACI were good with intraclass correlation of 0.93 (95% CI, 0.90–0.96) and intraclass correlation of 0.81 (95% CI, 0.71–0.88), respectively.

The LACI value is expressed as a percentage, and a higher LACI expresses greater disproportion between the LA and LV volumes at ventricular end-diastole reflecting greater impairment of left atrioventricular coupling. The theoretical framework underlying LACI in various subclinical pathophysiological settings is illustrated in Figure 2.

Outcomes

The MESA study outcome ascertainment protocols have been described in detail and are available online (www.mesa-nhlbi.org). Cardiovascular end points of interest were HF, AF, coronary heart disease (CHD) death, and hard CVD. In addition to MESA follow-up examinations every 2 years, a telephone interviewer contacted each participant (or representative) every 9 to 12 months to inquire about interim hospital admissions, CV outpatient diagnoses, and deaths. Two physicians reviewed all records for independent end point classification and assignment of event dates. Criteria for hard CVD outcomes included hard coronary events (including myocardial

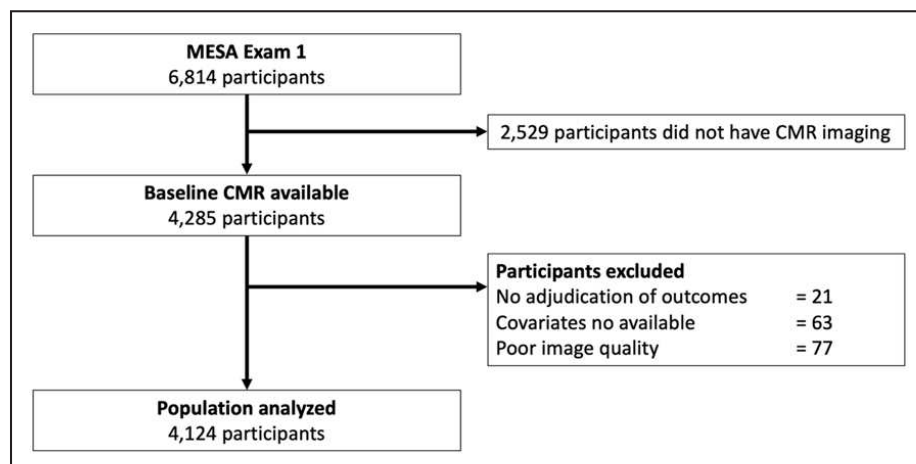


Figure 1. Flowchart of the study.

CMR indicates cardiovascular magnetic resonance; and MESA, Multi-Ethnic Study of Atherosclerosis.

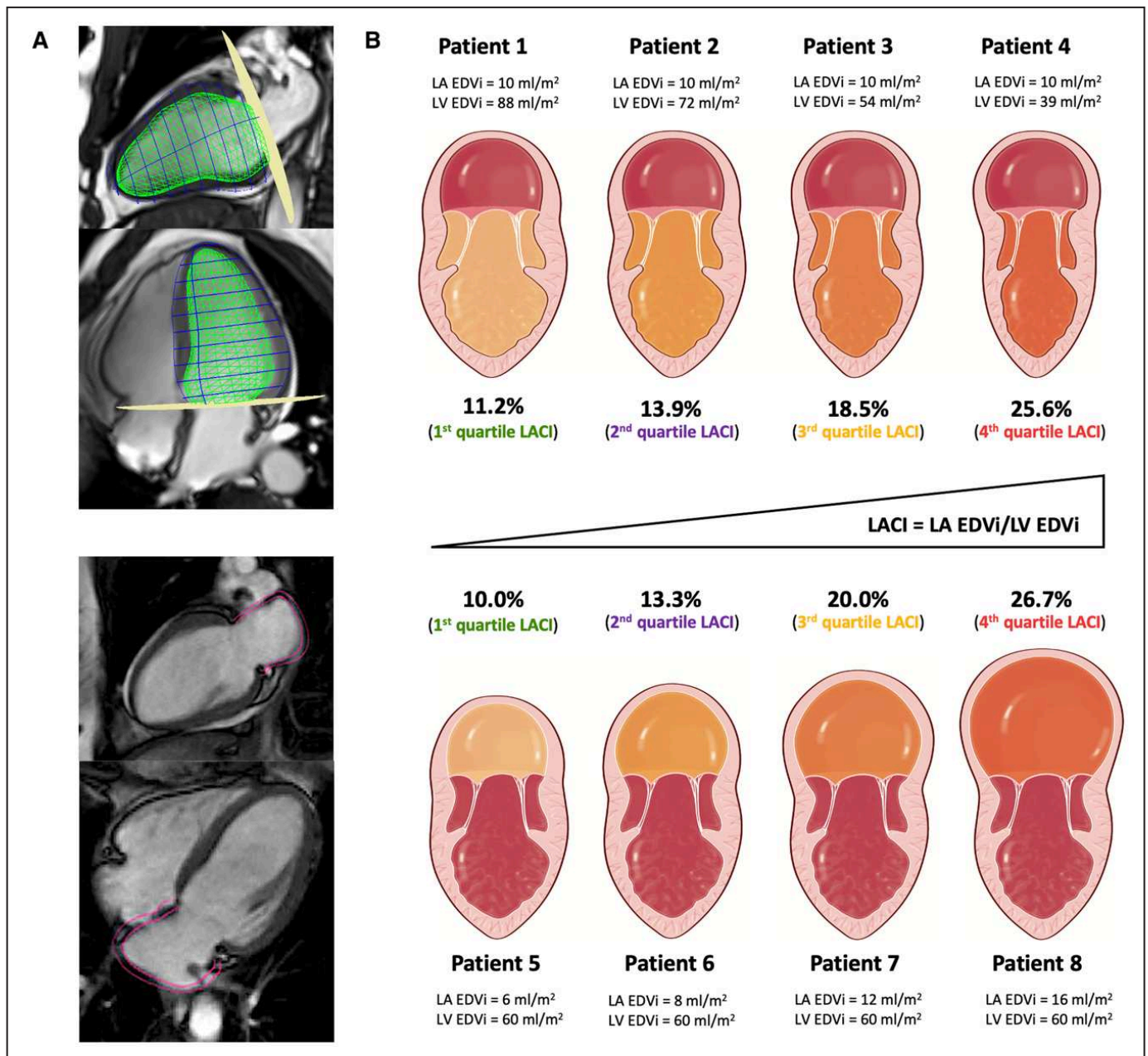


Figure 2. Schematic comparison of left atrioventricular coupling index (LACI) variations in different subclinical pathophysiological settings.

A, Illustrates the method to assess LACI by cardiovascular magnetic resonance (CMR) defined by the ratio between the left atrium (LA) end-diastolic volume and the left ventricle (LV) end-diastolic volume. A stack of short-axis cine images was acquired to encompass both ventricles and LV end-diastolic volume was measured using cardiac image modeler (CIM) software (green volume, **top**). LA end-diastolic volume was measured using multimodality tissue-tracking (MTT) software to track LA wall motion during the end-diastole (pink borders) in the 4-chamber and 2-chamber views (**bottom**). In the **B**, 4 patients from this cohort have the same normal value of LA end-diastolic volume indexed (EDVi; 10 mL/m²) but different normal LV EDVi values (**top**), and 4 other patients with the same normal value of LV EDVi (60 mL/m²) but different normal LA EDVi values (**bottom**). Although these values of LA EDVi or LV EDVi were identical, LACI increased significantly in all cases. These 8 patients belonged to one of the LACI quartiles with significantly different risk levels of cardiovascular events which were not detected by the value of LA EDVi or LV EDVi alone. A higher LACI reflects a higher dysfunction of the left atrioventricular coupling defined by a subclinical dilation of LA compared with LV.

infarction, resuscitated cardiac arrest, and death from coronary disease), in addition to fatal and nonfatal stroke. CHD death included myocardial infarction, chest pain within the 72 hours before death, or a history of CHD and the absence of a noncardiac cause of death. Criteria for HF as an end point included symptomatic HF diagnosed by a physician for a patient receiving medical treatment for HF and (1) pulmonary edema/congestion by chest x-ray and (2) dilated ventricle or

poor LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction. Criteria for AF as an end point required an AF diagnosis according to *International Classification of Diseases, Ninth Revision* codes. A detailed description of the criteria used for each end point is provided in the Text 3 in the [Data Supplement](#). If the first cardiovascular event claim occurred before the baseline study, the participant was excluded from the analyses.

Statistical Analyses

Baseline characteristics of study participants are presented as mean±SD or median (interquartile range) for continuous variables and as counts and percentages for categorical variables in Table 1. Comparisons employed the χ^2 or Fisher exact test for categorical variables and the Student *t* test or Mann–Whitney–Wilcoxon test, as appropriate, for continuous variables. We used Cox regression models to study the associations between LACI and the outcomes. The proportional hazard assumption was visually tested using Schoenfeld residuals (Figure S1). The cumulative risk of cardiovascular outcomes

over the follow-up years for the cohort, stratified by LACI quartiles, was determined using Kaplan–Meier curves, censored at most recent follow-up. Differences across quartiles were compared using the log-rank test. Following, the associations between LACI or all other LA and LV parameters and time-to-event were analyzed with multivariable Cox survival analyses, adjusting for traditional risk factors at baseline: age, sex, ethnicity, diabetes, systolic blood pressure, diastolic blood pressure, heart rate, current smoking, body mass index, antihypertensive therapy, lipid-lowering therapy, high-density lipoprotein cholesterol, total plasma cholesterol, and glomerular filtration rate.

Table 1. Population Characteristics of Participants at Baseline Before Occurrence of Events by Incident Event Categories (n=4124)

Parameters	No event (n=3426)	HF (n=220)	AF (n=213)	CHD death (n=198)	Hard CVD (n=443)
Age, y	60.3±9.9	68.2±8.8*	69.6±8.0*	70.1±8.5*	66.4±9.8*
Male, n (%)	1539 (44.9)	129 (58.6)*	123 (57.7)*	119 (60.1)*	273 (61.6)*
Ethnicity (White/Chinese American/Black/Hispanic), %	39/13/26/22	45/11/31/19*	55/8/19/18*	36/12/31/20	40/10/24/26
Hypertension, n (%)	1328 (38.8)	155 (70.5)*	127 (59.6)*	129 (65.2)*	269 (60.7)*
Systolic blood pressure, mm Hg	124±21	138±22*	134±24*	137±22*	135±22*
Diastolic blood pressure, mm Hg	72±10	74±12*	72.0±11	73±11	75±11*
Body mass index, kg/m ²	27.7±5.0	29.2±5.0*	28.3±5.0*	28.2±5.0	28.2±4.6*
Diabetes, n (%)	375 (10.9)	57 (25.9)*	32 (15.0)	51 (25.8)*	102 (23.0)*
Smoking status, n (%)	430 (12.6)	28 (12.7)	19 (8.9)	35 (17.7)*	73 (16.5)*
Heart rate, bpm	63±9	65±10*	62±10	64±10*	64±10*
Total cholesterol, mg/dL	195±36	190±33*	188±31*	190±39	193±35
HDL-cholesterol, mg/dL	52±15	49±13*	51±16	48.1±14*	48±14*
GFR, mL/min/1.73 m ² †	79.4±15.6	72.5±19.1*	70.7±17.1*	72.9±17.9*	74.6±18.0*
Chronic kidney disease, n (%)‡	239 (7.0)	60 (27.3)*	58 (27.2)*	65 (32.8)*	87 (19.6)*
Hypertension medication, n (%)	1112 (32.5)	132 (60.0)*	113 (53.1)*	109 (55.1)*	206 (46.5)*
Lipid-lowering medication, n (%)	517 (15.1)	41 (18.6)	39 (18.3)	42 (21.2)*	91 (20.5)*
NT-proBNP, pg/mL	39 (12–67)	159 (89–342)*	122 (69–256)*	118 (70–222)*	99 (64–298)*
Agatston score, mean±SD	92.2±283	390±719*	421±776*	341±616*	295±544*
Agatston score, median (IQR)	0 (0–78)	81 (0–366)*	88 (0–377)*	79 (0–353)*	74 (0–332)*
Framingham CVD risk, %	12.8±9.2	21.7±8.7*	20.0±9.4*	23.1±7.9*	20.6±9.1*
CHARGE-AF score	11.9±1.2	12.9±1.0*	13.0±1.0*	13.0±1.0*	12.5±1.1*
LV characteristics					
LV EDVi, mL/m ²	68.6±13.4	73.7±19.4*	70.5±17.7*	69.5±19.3	68.3±16.5
LVEF, %	62.6±5.9	59.9±8.1*	63.2±6.7	60.8±7.9*	61.5±7.1*
LV mass index, g/m ²	63.1±12.4	73.1±17.6*	68.2±15.6*	69.3±18.6*	68.3±15.7*
LVMVR, g/mL	0.93±0.17	1.02±0.21*	0.99±0.20*	1.02±0.21*	1.02±0.19*
LVGFI, %	40.3±6.2	36.4±7.2*	39.4±6.6	37.1±7.4*	37.5±6.6*
LA characteristics					
LA EDVi, mL/m ²	11.6±6.1	17.5±9.8*	19.7±11.4*	15.4±9.1*	13.8±7.6*
LA ESVi, mL/m ²	29.0±9.6	36.1±13.4*	38.8±15.3*	32.6±13.0*	31.0±11.5*
Peak LA strain, %	36.6±10.6	33.4±11.1*	32.1±9.9*	33.8±10.9*	35.0±11.4*
LACI, %	16.9±8.3	23.9±11.9*	27.9±13.7*	22.2±11.7*	20.4±10.6*

The comparisons with the no event population that were statistically significant with *P*<0.05 are shown in bold type. AF indicates atrial fibrillation; CHARGE-AF, Cohorts for Heart and Aging Research in Genomic Epidemiology AF CHD, coronary heart disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CVD, cardiovascular disease; EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; LA, left atrium; LACI, left atrioventricular coupling index; LV, left ventricle; LVEF, left ventricle ejection fraction; LVGFI, left ventricle global function index; LVMVR, LV mass/LV volume; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

†GFR was calculated by CKD-EPI method.

‡Chronic kidney disease was defined by glomerular filtration rate <60 mL/(min·1.73 m²).

We compared model discrimination using the C statistic. The additional predictive value of LACI was calculated by the C statistic increment, the categorical net reclassification improvement (NRI), and the integrative discrimination index (IDI),²⁶ and compared with the CHARGE-AF score,²⁷ Framingham score,²⁸ Agatston score,²⁹ and LA or LV parameters. NRI and IDI were computed at 10 years using the R package *survIDINRI*.³⁰ The survival tree method was used to determine the cutoff to transform LACI into a binary variable with the best predictive value for cardiovascular event occurrences. A 2-tailed *P* value <0.05 was considered statistically significant. All data were analyzed using R software, version 3.6.1 (R Project for Statistical Computing).

RESULTS

Study Population and Cardiovascular Events

Among the 6814 participants of the MESA cohort, 4124 (60.5%) underwent a baseline CMR examination with LA, LV, and outcome data available (mean age 61.5±10.1 years and 47.4% male participants). Among those, 42.5% of participants had hypertension, 12.6% had diabetes, 13.0% were current smokers, and the mean body mass index was 27.8±5.0 kg/m². At baseline, 35.4% of participants were on antihypertensive therapy and 15.9% on lipid-lowering medication. Population characteristics of all participants stratified by LACI quartiles are presented in Table S2. Population characteristics of all eligible participants at baseline are described in Table S3. Of note, eligible participants at baseline (n=6814) had a higher rate of both hypertension and hypertension medication than participants of this current study (n=4124). The baseline characteristics of the study population, divided into those who developed hard CVD (n=443, 10.7%), HF (n=220, 5.3%), AF (n=213, 5.2%), and CHD death (n=198, 4.8%) over a mean follow-up period of 13.0±3.2 years are presented in Table 1. Participants were followed during a mean follow-up of 11.2±3.7 years for AF and 16.2±1.1 years for other outcomes. Combining all pre-specified clinical events together and reporting only the first event for each patient, 698 (16.9%) participants had a cardiovascular event. All LA and LV functional parameters were lower in participants with cardiovascular events compared with those without cardiovascular events.

LACI Distribution and Relationship to Each LA and LV Parameter

In the entire population, mean LACI was 17.7±9.1% and the first to fourth quartiles of LACI were ≤11.4%; 11.4% to 16.3%; 16.3% to 22.4%; >22.4%, respectively (Figure S2), without differences between females and males (17.9±8.8% and 17.6±9.4%, respectively). Mean LACI was 16.9±8.3% in participants with no events. Regarding the definition of LACI, the LA end-diastolic volume was poorly correlated to LV end-diastolic volume (*R*²=0.15; Figure S3). All LA and LV parameters are reported in

Table 1 for participants with and without selected cardiovascular events. The relationship between LACI and values of other functional LV and LA parameters, and biomarkers are reported in the Figure S4. Notably, there was no relationship between LACI and systolic blood pressure at baseline (*P*=0.828, Figure S5).

Association of LACI With Incident AF

The results of unadjusted and adjusted Cox proportional hazard models for LACI and the main LA and LV parameters are indicated in Table 2 (other LA/LV parameters and biomarkers are presented in Table S4). LACI was positively associated with incident AF before and after adjustment for risk factors (adjusted hazard ratio [HR], 1.86 [95% CI, 1.69–2.04] per 1 SD increment; *P*<0.0001). When LACI was categorized in quartiles, a LACI value >22.4% was associated with AF incidence in comparison to the first quartile (<11.4%; log-rank *P*<0.0001; Figure 3).

Association of LACI With Incident HF

LACI was also positively associated with incident HF before and after adjustment for risk factors (adjusted HR, 1.50 [95% CI, 1.38–1.62] per 1 SD increment; *P*<0.0001; Table 2). The fourth quartile (>22.4%) was also associated with the HF incidence in comparison to the first quartile (<11.4%; log-rank *P*<0.0001; Figure 3).

Association of LACI With CHD Death

LACI was positively associated with CHD death before and after adjustment for risk factors (adjusted HR, 1.29 [95% CI, 1.15–1.45] per 1 SD increment; *P*<0.0001; Table 2). The fourth quartile (>22.4%) had a significantly higher risk of CHD death compared with the first quartile of LACI (<11.4%; log-rank *P*=0.0012; Figure 3).

Association of LACI With Hard CVD

After adjustment for risk factors, LACI was significantly associated with the hard CVD occurrence (adjusted HR, 1.23 [95% CI, 1.13–1.34] per 1 SD increment; *P*<0.0001; Table 2). The fourth quartile (>22.4%) had a significantly higher risk of CHD death compared with the first quartile of LACI (<11.4%; log-rank *P*=0.0004; Figure 3).

The global prognostic value of LACI was homogeneous regardless of the gender (Table S5) and of the systolic blood pressure level (Table S6).

Improvement in Risk Prediction With Addition of LACI

The multivariable model with LACI showed significant improvement to model discrimination and reclassification

Table 2. Univariable and Multivariable Analysis of CV Events Occurrence According to LACI and Other LA or LV Parameters

CMR parameters	Unadjusted			Adjusted		
	HR (95% CI)	P value	C-index (95% CI)	HR (95% CI)	P value	C-index (95% CI)
Incident AF						
LACI, % (per 1 SD)†	2.14 (1.97–2.32)	<0.0001*	0.76 (0.73–0.80)	1.86 (1.69–2.04)	<0.0001*	0.84 (0.81–0.86)
LACI cutoff >25%‡	7.32 (5.55–9.66)	<0.0001*	0.66 (0.63–0.69)	4.42 (3.29–5.92)	<0.0001*	0.81 (0.78–0.83)
LA EDVi, mL/m ² (per 1 SD)	1.83 (1.72–1.95)	<0.0001*	0.74 (0.71–0.78)	1.79 (1.66–1.94)	<0.0001*	0.83 (0.81–0.85)
LV EDVi, mL/m ² (per 1 SD)	1.09 (0.95–1.25)	0.2285	0.51 (0.46–0.55)	1.20 (1.05–1.38)	0.0084*	0.79 (0.76–0.82)
LVEF, % (per 1 SD)	1.13 (0.98–1.30)	0.1048	0.53 (0.49–0.58)	1.07 (0.93–1.23)	0.3640	0.79 (0.76–0.82)
LV mass, g/m ² (per 1 SD)	1.33 (1.19–1.50)	<0.0001*	0.58 (0.54–0.62)	1.26 (1.09–1.45)	0.0012*	0.79 (0.76–0.82)
Peak LA strain, % (per 1 SD)	0.57 (0.48–0.68)	<0.0001*	0.63 (0.59–0.67)	0.68 (0.57–0.81)	<0.0001*	0.80 (0.77–0.82)
Incident HF						
LACI, % (per 1 SD)†	1.70 (1.56–1.86)	<0.0001*	0.69 (0.66–0.73)	1.50 (1.38–1.62)	<0.0001*	0.82 (0.80–0.85)
LACI cutoff >25%‡	4.39 (3.26–5.91)	<0.0001*	0.60 (0.57–0.63)	2.71 (1.98–3.71)	<0.0001*	0.80 (0.77–0.83)
LA EDVi, mL/m ² (per 1 SD)	1.57 (1.47–1.67)	<0.0001*	0.68 (0.65–0.72)	1.47 (1.33–1.63)	<0.0001*	0.82 (0.80–0.85)
LV EDVi, mL/m ² (per 1 SD)	1.38 (1.21–1.57)	<0.0001*	0.56 (0.52–0.61)	1.48 (1.34–1.63)	<0.0001*	0.81 (0.79–0.84)
LVEF, % (per 1 SD)	0.67 (0.60–0.75)	<0.0001*	0.61 (0.56–0.65)	0.66 (0.60–0.74)	<0.0001*	0.81 (0.79–0.84)
LV mass, g/m ² (per 1 SD)	1.65 (1.52–1.79)	<0.0001*	0.66 (0.62–0.70)	1.63 (1.46–1.83)	<0.0001*	0.82 (0.79–0.84)
Peak LA strain, % (per 1 SD)	0.68 (0.58–0.80)	<0.0001*	0.61 (0.57–0.65)	0.84 (0.72–0.98)	0.0303*	0.80 (0.77–0.83)
CHD death						
LACI, % (per 1 SD)†	1.53 (1.38–1.70)	<0.0001*	0.64 (0.60–0.68)	1.29 (1.15–1.45)	<0.0001*	0.84 (0.81–0.86)
LACI cutoff >25%‡	2.86 (2.02–4.04)	<0.0001*	0.59 (0.55–0.62)	1.69 (1.18–2.42)	0.0044*	0.83 (0.80–0.85)
LA EDVi, mL/m ² (per 1 SD)	1.40 (1.28–1.53)	<0.0001*	0.61 (0.57–0.66)	1.29 (1.16–1.43)	<0.0001*	0.84 (0.81–0.86)
LV EDVi, mL/m ² (per 1 SD)	1.00 (0.87–1.16)	0.9741	0.47 (0.42–0.52)	1.19 (1.04–1.37)	0.0103*	0.83 (0.80–0.85)
LVEF, % (per 1 SD)	0.76 (0.67–0.86)	<0.0001*	0.55 (0.51–0.60)	0.76 (0.67–0.86)	<0.0001*	0.83 (0.80–0.85)
LV mass, g/m ² (per 1 SD)	1.42 (1.27–1.59)	<0.0001*	0.57 (0.52–0.62)	1.33 (1.15–1.53)	0.0001*	0.83 (0.81–0.86)
Peak LA strain, % (per 1 SD)	0.73 (0.62–0.87)	<0.0001*	0.59 (0.55–0.63)	0.92 (0.79–1.07)	0.2720	0.83 (0.80–0.85)
Hard CVD						
LACI, % (per 1 SD)†	1.35 (1.25–1.46)	<0.0001*	0.59 (0.57–0.62)	1.23 (1.13–1.34)	<0.0001*	0.76 (0.74–0.78)
LACI cutoff >25%‡	2.43 (1.90–3.10)	<0.0001*	0.57 (0.55–0.59)	1.76 (1.36–2.28)	<0.0001*	0.75 (0.73–0.78)
LA EDVi, mL/m ² (per 1 SD)	1.24 (1.15–1.33)	<0.0001*	0.57 (0.54–0.60)	1.16 (1.06–1.26)	0.0005*	0.75 (0.73–0.77)
LV EDVi, mL/m ² (per 1 SD)	0.89 (0.81–0.99)	0.0293*	0.54 (0.51–0.57)	0.98 (0.88–1.08)	0.6375	0.75 (0.73–0.77)
LVEF, % (per 1 SD)	0.84 (0.77–0.92)	0.0001*	0.54 (0.51–0.57)	0.88 (0.80–0.96)	0.0039*	0.75 (0.73–0.77)
LV mass, g/m ² (per 1 SD)	1.35 (1.25–1.46)	<0.0001*	0.58 (0.55–0.60)	1.18 (1.07–1.31)	0.0014*	0.75 (0.73–0.77)
Peak LA strain, % (per 1 SD)	0.85 (0.77–0.94)	0.0002*	0.55 (0.53–0.58)	1.00 (0.91–1.10)	0.9916	0.75 (0.73–0.77)

All LV parameters, LA parameters and LACI values were normalized according to the following formula: (parameter–mean value)/SD. Adjusted model included age, sex, ethnicity, diabetes, systolic blood pressure, diastolic blood pressure, heart rate, current smoking, body mass index, antihypertensive therapy, lipid-lowering therapy, HDL-cholesterol, total plasma cholesterol, glomerular filtration rate. AF indicates atrial fibrillation; CHD, coronary heart disease; CMR, cardiovascular magnetic resonance; CVD, cardiovascular disease; EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; HDL, high-density lipoprotein; HF, heart failure; HR: hazard ratio; LA, left atrium; LACI, left atrioventricular coupling index; LV, left ventricle; and LVEF, left ventricle ejection fraction.

†LACI used as continuous variable.

‡LACI used as binary variable defined by a cutoff >25%.

compared with the multivariable model with traditional risk factors to predict incident AF (C statistic: 0.84 versus 0.79; NRI, 0.637; IDI, 0.082), incident HF (C statistic: 0.82 versus 0.80; NRI, 0.528; IDI, 0.024), CHD death (C statistic: 0.84 versus 0.83; NRI, 0.350; IDI, 0.005), and hard CVD (C statistic: 0.77 versus 0.76; NRI, 0.227; IDI, 0.009). LACI also had better a discrimination and reclassification for AF and hard CVD compared with the multivariable model with each LA or LV parameter (Table S7). Regarding the prediction of AF, LACI had better

discrimination and reclassification compared with the CHARGE-AF score (C statistic: 0.84 versus 0.79; NRI, 0.637 versus 0.255; IDI, 0.082 versus 0.005). Discrimination and reclassification associated with LACI to other biomarkers and scores are presented in Table S8.

Prognostic Value of Binary LACI

The best LACI cutoff was >29% to predict incident AF, >27%, to predict incident HF, >26% to predict CHD

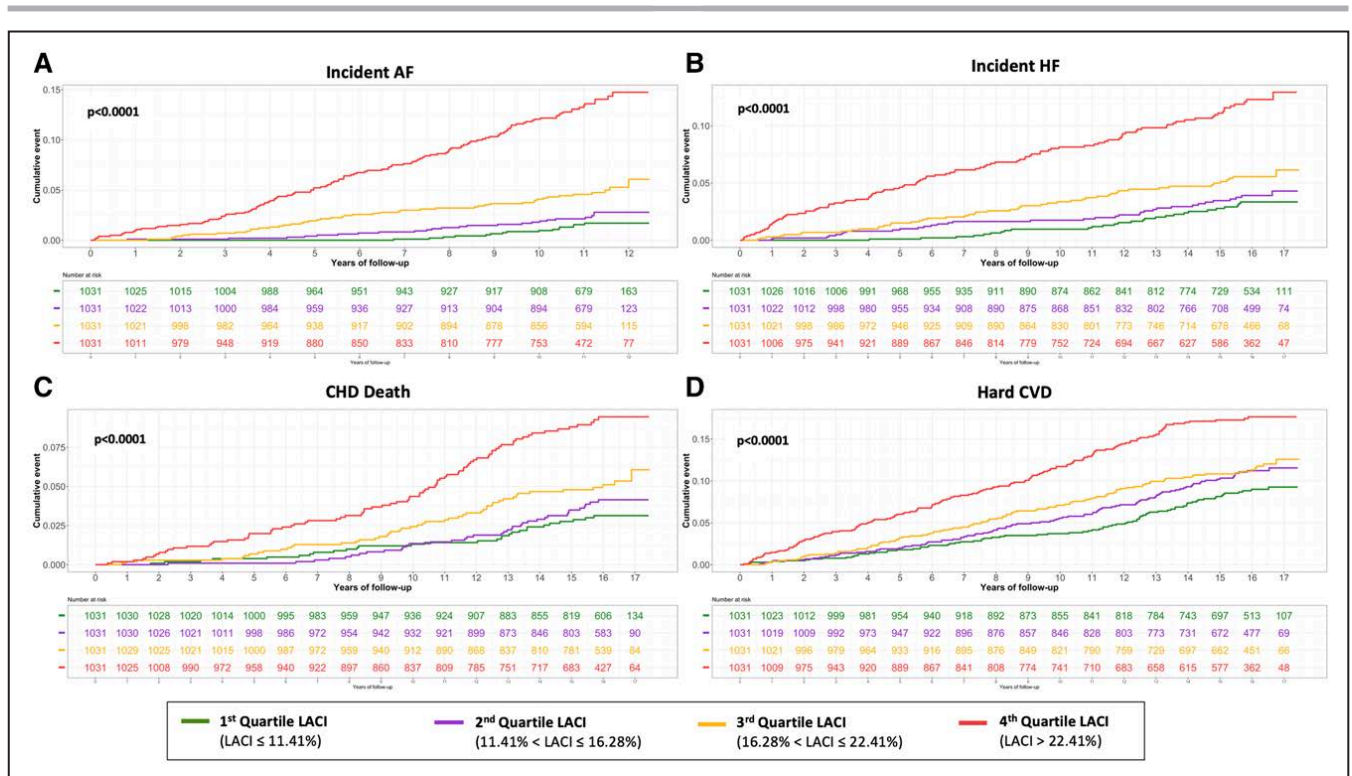


Figure 3. Kaplan-Meier survival curves for cardiovascular events stratified by left atrioventricular coupling index (LACI) quartiles.

Kaplan-Meier survival curves for incident atrial fibrillation (AF; **A**), incident heart failure (HF; **B**), coronary heart disease (CHD) death (**C**), and hard cardiovascular disease (CVD; **D**) by left atrioventricular coupling index (LACI) quartiles. The cumulative hazard was systematically significantly greater in the fourth quartile compared with the other quartiles for each outcome (logrank for difference; $P < 0.0001$).

death, and $>27\%$ to predict hard CVD (Table S9). Using the composite outcome cutoff including incident HF, incident AF, CHD death, and hard CVD, an increased LACI of $>25\%$ was independently associated with an increased occurrence of AF (adjusted HR, 4.42 [95% CI, 3.29–5.92]), HF (adjusted HR, 2.71 [95% CI, 1.98–3.71]), CHD death (adjusted HR, 1.69 [95% CI, 1.18–2.42]),

and hard CVD (adjusted HR, 1.76 [95% CI, 1.36–2.28]; $P < 0.0001$ for all; Table 2 and Figure 4).

DISCUSSION

In this study, we demonstrate the predictive value of a novel left atrioventricular coupling index, LACI, for

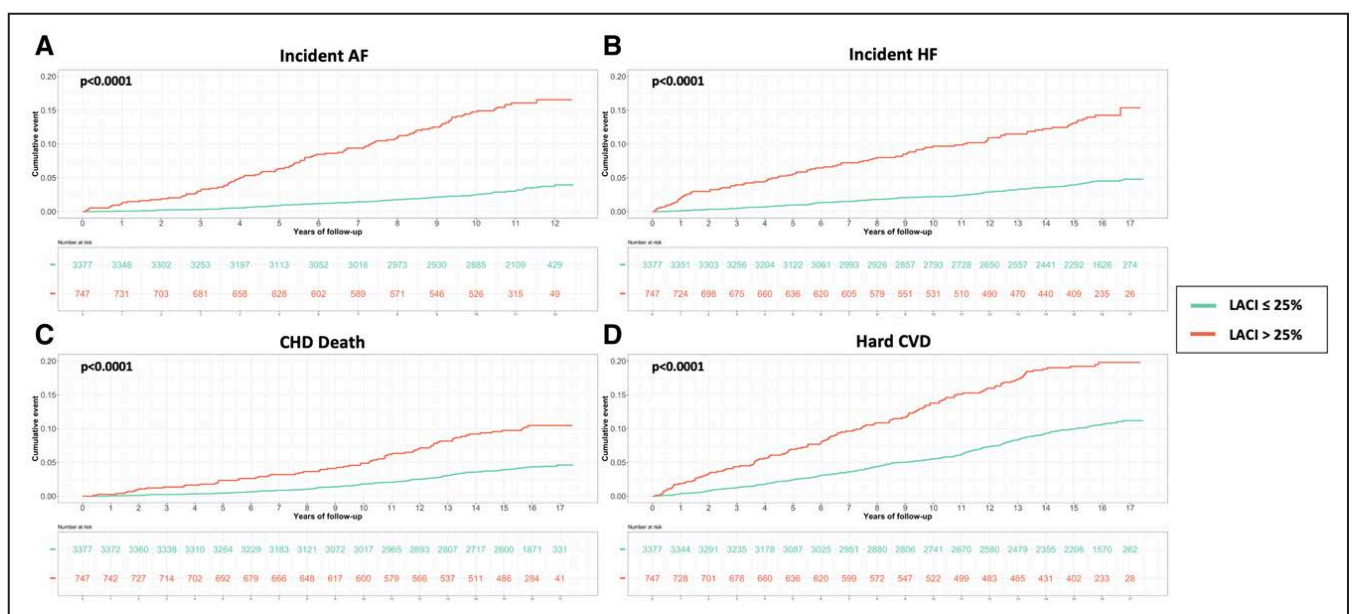


Figure 4. Kaplan-Meier survival curves for cardiovascular events stratified by left atrioventricular coupling index (LACI) $>25\%$. Kaplan-Meier survival curves for incident atrial fibrillation (AF; **A**), incident heart failure (HF; **B**), coronary heart disease (CHD) death (**C**), and hard cardiovascular disease (CVD; **D**) stratified by left atrioventricular coupling index (LACI) $>25\%$.

incident AF, HF, CHD death, and hard CVD in a multi-ethnic population, aged 45 to 84 years, free of clinical CVD at enrollment. Indeed, LACI showed the greatest association with those CV outcomes, improving model discrimination and reclassification of CV event risk. To our knowledge, the prognostic value of this left atrioventricular coupling index, and the incremental model discrimination of LACI over and above traditional clinical risk factors have not been previously reported.

LACI identifies an earlier stage of LA remodeling when compared with individual LA parameters, having a higher prognostic value for predicting CV events after adjustment for traditional risk factors. Therefore, relating LA to LV volume, LACI improves model discrimination and reclassification in predicting the risk of outcomes relative to such individual parameters measured separately, and saves time in clinical routine with a fast and simple measurement. Notably, the prognostic value of LACI was independent of participants' ethnicity. These results are consistent with a prior CMR study performed in 40 healthy individuals that investigated the effects of aging on left atrioventricular coupling and LV filling.²⁰ The oldest individuals had larger LA and smaller LV volumes with larger LA/LV end-diastolic volume ratio ($27\pm 6\%$ versus $19\pm 3\%$; $P<0.001$) and preserved LVEF. Moreover, in a canine model of early-stage hypertensive HF with preserved LVEF, left atrioventricular coupling assessed by CMR was impaired and the curvilinear LA end-reservoir pressure-volume relationship was shifted upward and leftward, indicating reduced LA compliance.³¹ More recently, Backhaus et al¹⁹ suggested a potential prognostic value for atrioventricular mechanical coupling in predicting CV events in a clinical study of 795 patients with acute coronary syndrome.

LA size has been conceived as a barometer of LV filling pressure and diastolic function.¹⁶ Recent investigation has suggested that measuring LA end-diastolic volume^{10,11} or changes in LA end-diastolic volume³² may be more robust than maximal LA volume (at LV end-systole) to predict CVD. Moreover, a rise in LA end-diastolic volume has been reported as the best LA parameter to correlate with elevation of LV filling pressures.¹⁰ Such findings reflect the important interaction that exists between LA and LV performance, particularly during LV diastole, in the absence of mitral valve disease.^{15,16}

Therefore, our study highlights the prognostic importance of atrioventricular coupling reflected by intricate hemodynamic interactions between LA and LV during LV diastole.¹⁸ At the beginning of LV diastole, passive filling begins, characterized by a rotating blood flow pattern in the LA, that gradually decreases and then stops when pressures between the 2 chambers are equalized. This passive filling pattern results in an early diastolic blood flow vortex formation inside the LV cavity, even stronger than the original flow rotational pattern in the LA. The resultant buildup of kinetic energy expands the LV to

greater diastolic volume.¹⁷ During the diastasis period, the transmitral flow velocity is transiently reduced before the onset of active filling, which further energizes vortex formation pattern up to the end of LV diastole. Such blood flow vortex contributes to redirecting the incoming LA inflow towards the LV outflow tract, priming the LV by stretching cardiomyocytes and maximizing preload before the onset of LV systolic contraction.³³ Such mechanisms underlie the important hemodynamic interaction of the LA and LV at end diastole, possibly explaining the particular prognostic value of LACI, that is, left AV coupling measured at that moment. All these reasons explain the genesis of combining these 2 measurements of atrial and ventricular end-diastolic volume, obtained simultaneously, in the conception of LACI, allowing through a simple measurement, to capture the combined LA and LV performance.

The prevalence of AF is estimated to be up to 2% in the United States, with projected doubling by 2030. In this study, LACI was a stronger independent predictor of incident AF than the CHARGE-AF score and the individual LA or LV parameters, resulting in improved reclassification and discrimination. The increase in LA volume relative to that of the LV at end-diastole reflects impaired LV compliance, leading to a reduction of LA pump function, which has been proposed as an independent predictor of incident AF.¹⁸ Regarding other CV outcomes, LACI showed greater ability to predict CHD death than the Framingham and Agatston scores. We also investigated the best LACI cutoff points to predict different CV outcomes and found slightly different best cutoff points with $>29\%$ for incident AF, $>27\%$ for incident HF, $>26\%$ for CHD death, and $>27\%$ for hard CVD. This suggests different pathophysiological mechanisms involving atrioventricular coupling for different outcomes. LACI $>25\%$ was the best cutoff for the composite of all four CV outcomes. Further studies will need to assess the clinical value of adding LACI to cardiovascular event prediction models in general population.

Limitations

Among our study limitations, the general applicability of these findings may be limited by selection and survivor biases. Indeed, participants had no known CVD at baseline and therefore, older participants undergoing CMR in this cohort represent a healthier sample than the older general population. In addition, LACI was investigated to be a primary prevention tool in the early detection of the CVD risk in asymptomatic patients without known CVD. Indeed, in a patient with CVD and who presents with both LA and LV enlargements, LACI would not be the best assessment tool. For all these reasons, the extension of these results to populations with prevalent disease would require additional investigation. Moreover, incident AF was identified based on diagnosis discharge codes,

which may underestimate incident AF, as many AF cases can be asymptomatic. However, a validation sub-study on 45 MESA participants with the classification of AF based upon hospital discharge codes confirmed the diagnosis of AF in 93% of hospitalizations, implying high specificity for the adjudicated outcome.³⁴

HF was not differentiated into HF with preserved or reduced LVEF due to the relatively low number of events. In addition, the exclusion of participants with no adjudicated outcome, with unavailable CMR data, or poor quality of images, could have introduced bias in the study. However, these excluded participants tended to be older and had more risk factors. Therefore, we hypothesize that their inclusion would more likely increase the strength of our associations. We used 2 instead of 3-dimensional methods to measure LA volumes, which may have underestimated true volumes by 11.5% to 20%.³⁵ However, this method has been widely used and validated in clinical studies.^{23,24} Knowing that CMR is not a widely accessible test in routine, the use of LACI as a screening tool in the general population should be investigated in echocardiography, particularly with the advent of 3-dimensional echocardiography. In addition, further studies should also evaluate the incremental prognostic value of LACI compared with other biomarkers such as troponin, NT-proBNP (N-terminal pro-B-type natriuretic peptide) or interleukin 6, and diastolic dysfunction parameters using echocardiography. Residual confounding cannot be completely eliminated from this cross-sectional study, because only the traditional risk factors assessed at baseline were analyzed in the final models without any utilization of time-varying covariates, with incomplete accounting for traditional risk factor covariate status. Beyond left atrioventricular coupling, this study did not include analysis of left ventriculoarterial coupling. Further studies may investigate the relationship between these 2 couplings. Finally, while the mechanisms by which cardiovascular events are associated with left atrioventricular coupling derangements are not entirely elucidated by these observational data, the study provides important clues to the pathophysiology of cardiovascular events.

Conclusions

In a large multi-ethnic study population free of clinical CVD at baseline, greater LACI measured by CMR imaging was associated with high risk of incident AF, HF, CHD death, and hard CVD during a 13-year average follow-up. The addition of LACI to risk prediction models for these outcomes showed improvement to model discrimination and reclassification of cardiovascular event risks. Future studies should validate these findings to better understand the role of left atrioventricular coupling in the pathophysiology of cardiovascular events.

Perspectives

Using CMR data, a new left atrioventricular coupling index was identified in a large cohort of patients without CVD at enrolment: the MESA. This index was independently associated with the occurrence of cardiovascular events, showing an incremental long-term prognostic value over and above traditional clinical risk factors. The concept of left atrioventricular coupling is supported by this coupling index which has a better prognostic value than individual LA or LV parameters measured separately.

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Partie 3 :

Étude n°2 : Déterminants impliqués dans le couplage auriculo-ventriculaire gauche cardiaque

Determinants of left atrioventricular coupling index: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Après avoir décrit pour la première fois un index de couplage auriculo-ventriculaire gauche comme outil de stratification pronostique avec une valeur pronostique forte pour prédire le risque d'évènements cardiovasculaires dans notre étude n°1, une nouvelle étude s'est intéressée à l'exploration des déterminants impliqués dans ce couplage auriculo-ventriculaire gauche. Cette deuxième étude, plus exploratoire et translationnelle, se propose d'utiliser le LACI comme marqueur reflétant le fonctionnement du couplage auriculo-ventriculaire gauche afin d'identifier les paramètres cliniques, biologiques et d'imagerie impliqués dans le bon fonctionnement de ce couplage.

Ainsi l'objectif de cette nouvelle étude est d'identifier les déterminants de ce nouvel indice, le LACI, et de sa variation annuelle sur 10 ans (Δ LACI), mesurés par imagerie par IRM cardiovasculaire, afin de mieux comprendre les paramètres qui régissent ce couplage auriculo-ventriculaire gauche.

Dans le cadre de l'étude MESA (*Multi-Ethnic Study of Atherosclerosis*), 2112 participants à l'étude, sans maladie cardiovasculaire au recrutement, ont fait l'objet d'une mesure de leur LACI évalué par IRM cardiaque au départ (2000-2002) et 10 ans plus tard (2010-2012). Le LACI a été défini comme le rapport entre le volume télédiastolique de l'OG et le volume télédiastolique du VG. Des analyses de régression linéaire ont été effectuées pour identifier les déterminants indépendants du LACI mesuré au début de l'étude ou du Δ LACI.

Chez les 2112 participants (59 ± 9 ans ; 47% d'hommes), après ajustement pour toutes les covariables, l'âge était indépendamment associé à la fois au LACI mesuré au début de l'étude ($R^2 = 0,10$) et au Δ LACI ($R^2 = 0,15$; tous deux $p < 0,001$). Les Afro-Américains avaient la valeur de LACI mesurée au début de l'étude, la plus élevée ($18,0 \pm 7,7$ %). Bien qu'il n'y ait pas de différence de la valeur du LACI mesurée au début de l'étude entre les femmes et les hommes ($p = 0,19$), le Δ LACI était plus élevé chez les femmes que chez les hommes ($1,0 \pm 1,1$ contre $0,8 \pm 1,0$ %/an ; $p < 0,001$). Le diabète et un IMC plus élevé étaient indépendamment associés à la valeur du LACI mesurée au début de l'étude ($p < 0,001$ dans les deux cas). Le LACI mesuré au début de l'étude était indépendamment associé aux marqueurs de fibrose du myocarde VG mesuré par IRM cardiaque (T1 mapping natif : $R^2 = 0,11$ [$p = 0,038$] ; et volume extracellulaire : $R^2 = 0,08$ [$P = 0,035$]) et de la valeur du NT-proBNP ($R^2 = 0,10$; $p < 0,001$), mais n'était pas associé aux marqueurs de l'inflammation.

En résumé, cette deuxième étude réalisée dans une population de participants indemnes de maladie cardiovasculaire clinique, a mis en évidence des résultats importants concernant les déterminants du LACI à l'inclusion, et sa variation annuelle sur 10 ans (LACI) comme marqueurs du couplage auriculo-ventriculaire gauche :

- Une augmentation l'âge était indépendamment associée à une augmentation à la fois du LACI et du Δ LACI après ajustement pour toutes les covariables ;
- Bien qu'il n'y ait pas de différence dans le LACI entre les femmes et les hommes, le Δ LACI était plus élevé chez les femmes que chez les hommes ;
- En ce qui concerne l'ethnicité des participants, les Afro-Américains avaient la valeur LACI plus élevée, tandis que les participants chinois avaient la plus faible ;
- Le diabète et un IMC plus élevé étaient indépendamment associés à LACI ;
- Le LACI était indépendamment associé aux marqueurs de fibrose myocardique LV et à la concentration de NT-proBNP, mais il n'y avait aucune association entre LACI et les biomarqueurs de l'inflammation ou la troponine T cardiaque à haute sensibilité.



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CLINICAL RESEARCH

Determinants of left atrioventricular coupling index: The Multi-Ethnic Study of Atherosclerosis (MESA)[☆]

Déterminants de l'indice de couplage auriculo-ventriculaire gauche : l'étude multiethnique de l'athérosclérose (MESA)

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KEYWORDS

Cardiac magnetic resonance;
Left atrium;

Summary

Background. — Recent studies have described a novel left atrioventricular coupling index (LACI), which had a better prognostic value in predicting cardiovascular events than individual left atrial (LA) or left ventricular (LV) variables.

Abbreviations: BMI, body mass index; CMR, cardiac magnetic resonance; CVD, cardiovascular disease; ECV, extracellular volume; LA, left atrium/atrial; LACI, left atrioventricular coupling index; Δ LACI, annualized change in LACI over 10 years; LV, left ventricle/ventricular; MESA, Multi-Ethnic Study of Atherosclerosis; MVR, mass-to-volume ratio; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

[☆] Tweet: First paper to investigate the determinants of left atrioventricular coupling using a new index, the LACI defined by cardiac MRI! Study from MESA by @PezelT and @HopkinsMedicine.

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Left ventricle;
Coupling;
Multi-Ethnic Study of
Atherosclerosis
(MESA)

Aims. – To identify determinants of LACI and its 10-year annual change (Δ LACI), measured by cardiac magnetic resonance (CMR), and to better understand the variables governing this left atrioventricular coupling.

Methods. – In the Multi-Ethnic Study of Atherosclerosis, 2112 study participants, free from cardiovascular disease at baseline, had LACI assessed by CMR imaging at baseline (LACI_{Baseline}; 2000–2002) and 10 years later (2010–2012). The LACI was defined as the ratio of LA to LV end-diastolic volumes. Linear regression analyses were performed to identify independent determinants of LACI_{Baseline} and Δ LACI.

Results. – In the 2112 participants (mean age 58.8 ± 9.1 years; 46.6% male), after adjustment for all covariates, age was independently associated with LACI_{Baseline} ($R^2 = 0.10$, slope = 0.16) and Δ LACI ($R^2 = 0.15$, slope = 0.008; both $P < 0.001$). African Americans had the highest LACI_{Baseline} value ($18.0 \pm 7.7\%$). Although there was no difference in LACI_{Baseline} between women and men ($P = 0.19$), Δ LACI was higher in women (1.0 ± 1.1 vs $0.8 \pm 1.1\%/year$; $P < 0.001$). Diabetes and higher body mass index (BMI) were independently associated with LACI_{Baseline} (both $P < 0.001$). LACI_{Baseline} was independently associated with LV myocardial fibrosis markers (native T1: $R^2 = 0.11$, slope = 0.09 [$P = 0.038$]; extracellular volume: $R^2 = 0.08$, slope = 0.28 [$P = 0.035$]) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) concentration ($R^2 = 0.10$, slope = -1.11 ; $P < 0.001$), but was not associated with interleukin 6 or high-sensitivity C-reactive protein.

Conclusions. – Age, sex, ethnicity, diabetes and BMI were independent determinants of LACI. LACI was independently associated with myocardial fibrosis markers and NT-proBNP concentration.

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MOTS CLÉS

Imagerie par
résonance
magnétique
cardiaque ;
Oreillette gauche ;
Ventricule gauche ;
Couplage ;
Étude Multi-Ethnique
de l'Athérosclérose
(MESA)

Résumé

Contexte. – Des études récentes ont décrit un nouvel indice de couplage auriculo-ventriculaire gauche (LACI), qui avait une meilleure valeur pronostique que la mesure individuelle de tous les paramètres structurels ou de fonction de l'oreillette gauche (OG) ou du ventricule gauche (VG) pour prédire la survenue d'événements cardiovasculaires.

Objectifs. – Identifier les déterminants de ce nouvel indice, le LACI, et de sa variation annuelle sur 10 ans (Δ LACI), mesurés par imagerie par résonance magnétique (IRM) cardiovasculaire, et mieux comprendre les paramètres régissant ce couplage auriculo-ventriculaire gauche.

Méthodes. – Dans le cadre de l'étude MESA (Multi-Ethnic Study of Atherosclerosis), 2112 participants à l'étude, sans maladie cardiovasculaire au recrutement, ont eu une mesure de leur LACI évalué par IRM cardiaque au départ (2000–2002) et 10 ans plus tard (2010–2012). Le LACI a été défini comme le rapport entre le volume télé-diastolique de l'OG et le volume télé-diastolique du VG. Des analyses de régression linéaire ont été effectuées pour identifier les déterminants indépendants du LACI mesuré au début de l'étude ou du Δ LACI.

Résultats. – Chez les 2112 participants ($58,8 \pm 9,1$ ans; 46,6 % d'hommes), après ajustement pour toutes les covariables, l'âge était indépendamment associé à la fois au LACI mesuré au début de l'étude ($R^2 = 0,10$) et au Δ LACI ($R^2 = 0,15$; tous deux $p < 0,001$). Les Afro-Américains avaient la valeur de LACI mesurée au début de l'étude la plus élevée ($18,0 \pm 7,7$ %). Bien qu'il n'y ait pas de différence de la valeur du LACI mesuré au début de l'étude entre les femmes et les hommes ($p = 0,19$), le Δ LACI était plus élevé chez les femmes que chez les hommes ($1,0 \pm 1,1$ contre $0,8 \pm 1,0$ %/an; $P < 0,001$). Le diabète et un IMC plus élevé étaient indépendamment associés à la valeur du LACI mesurée au début de l'étude ($p < 0,001$ dans les deux cas). Le LACI mesuré au début de l'étude était indépendamment associé aux marqueurs de fibrose du myocarde VG (T1 natif: $R^2 = 0,11$ [$p = 0,038$]; et volume extracellulaire: $R^2 = 0,08$ [$P = 0,035$]) et de la valeur du NT-proBNP ($R^2 = 0,10$; $p < 0,001$), mais n'était pas associé aux marqueurs de l'inflammation.

Conclusions. – L'âge, le sexe, l'origine ethnique, le diabète et l'IMC étaient des déterminants indépendants de la valeur du LACI mesuré au début de l'étude. Le LACI était indépendamment associée aux marqueurs de fibrose myocardique du VG et de la valeur du NT-proBNP.

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Background

Given the important mediceconomic burden associated with cardiovascular disease (CVD) [1], it is crucial to develop simple and powerful variables in clinical routines for stratifying the CVD risk of individuals in primary prevention. Using cardiovascular imaging, several left ventricular (LV) structural and functional variables have shown prognostic value in predicting the occurrence of cardiovascular events [2,3]. Some left atrial (LA) structural and functional variables have also consistently exhibited prognostic value in predicting cardiovascular events [4,5]. The left atrium (LA) and left ventricle (LV) interact throughout the cardiac cycle. Knowing this close physiological relationship between the LA and LV [6,7], our working group has recently developed, from the Multi-Ethnic Atherosclerosis Study (MESA) cohort, a novel left atrioventricular coupling index (LACI), defined as the ratio between the LA end-diastolic volume and the LV end-diastolic volume using cardiac magnetic resonance (CMR) [8]. We demonstrated the incremental prognostic value of LACI for predicting incident heart failure, incident atrial fibrillation, hard CVD and cardiovascular death, along with traditional risk factors. More recently, using a longitudinal analysis, our team has shown the incremental prognostic value of annualized change in LACI over 10 years (Δ LACI), along with traditional risk factors, which had a better prognostic value than individual changes in LA or LV variables measured separately to predict incident heart failure [9] and incident atrial fibrillation [10]. All of these findings support the physiological concept of left atrioventricular coupling by this LA/LV coupling index, which has a better prognostic value than individual LA or LV variables measured separately.

Beyond the prognostic value of this index, it is important to identify the determinants of LACI, to better understand the factors involved in the physiology of this LA/LV coupling. However, to our knowledge, because of a lack of tools to measure LA/LV coupling, no research has explored the potential determinants of this coupling. Therefore, the aim of this study was to identify the determinants of LACI as a left atrioventricular coupling marker, and its 10-year annual change (Δ LACI), using the MESA, to better understand the variables governing this left atrioventricular coupling.

Methods

Study population

The MESA is a prospective population-based multi-ethnic (African American, White, Chinese and Hispanic) cohort study of subclinical CVD. The details of the study design have been described previously [11]. In summary, between 2000 and 2002 (Exam 1), 6814 men and women aged 45–84 years who were free of clinical CVD at enrolment were recruited from six field centres in the USA (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St. Paul, MN). Exam 1 was followed by Exam 2 (2002–2004), Exam 3 (2004–2005), Exam 4 (2005–2007) and Exam 5 (2010–2012). Participants with significant valvular disease at baseline or between the two CMR examinations were excluded. The methodology for collection of baseline characteristics is detailed in Appendix A. All participants

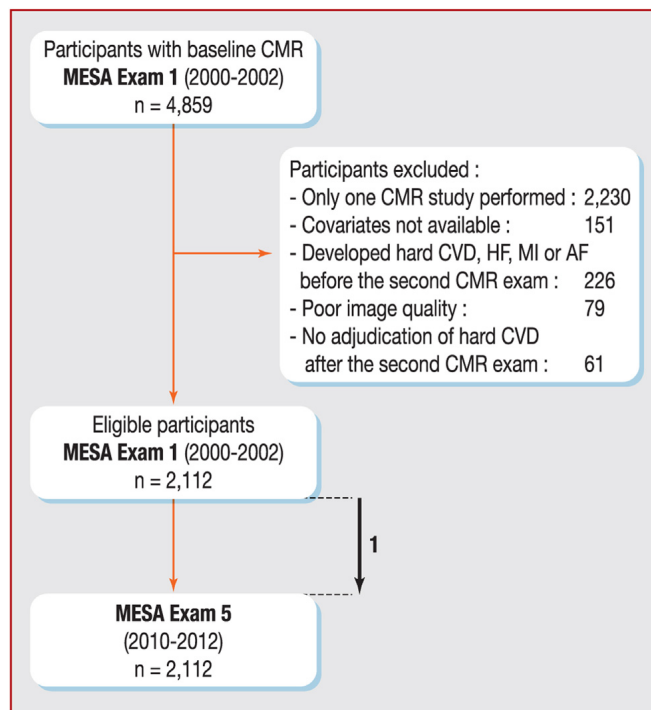


Figure 1. Flowchart of the study. 1 = mean time between the baseline and second cardiac magnetic resonance (CMR) examinations: 9.5 ± 0.6 years. AF: atrial fibrillation; CVD: cardiovascular disease; HF: heart failure; MESA: Multi-Ethnic Study of Atherosclerosis; MI: myocardial infarction.

provided written informed consent. All study protocols were approved by the institutional review boards of each participating field centre.

A flowchart of the MESA population investigated in the current study is shown in Fig. 1. Participants were excluded: (1) if they did not have the second CMR examination; (2) if their images were of insufficient quality to allow the measurement of volumes; or (3) if they developed any cardiovascular events between Exams 1 and 5. The collection of outcomes is described in Appendix B. Of the 4859 participants with baseline CMR that included LA volume assessment (Exam 1), 2112 participants underwent a second CMR examination at Exam 5 after a mean time of 9.5 ± 0.6 years, and were included in the study.

CMR protocol and image analysis

The CMR protocol has been described previously [12]. Briefly, CMR was performed using 1.5-Tesla scanners (Appendix C). Long-axis cine images were obtained from two-chamber and four-chamber views using fast gradient-echo pulse sequences. A stack of short-axis cine images was acquired, and LV end-diastolic volume was measured using cardiac image modelling software (CIM version 6.0, University of Auckland, New Zealand). The complete CMR protocol, as well as details of the image analysis and data quality control have been published previously [12]. Multimodality tissue tracking (MTT) software, version 6.0 (Toshiba Medical Systems, Tokyo, Japan) was used to quantify LA volume and strain from two- and four-chamber cine CMR images (Appendix D). This method has been validated previously, with good-to-excellent intra- and inter-reader

reproducibility [13–15]. Using the marked points, the software creates endocardial borders, and then tracks LA tissue in subsequent frames. The endocardial and epicardial contours generated by the software are then followed by the operator during the cardiac cycle.

LACI

As recently described by our working group [8], LACI was calculated using the following formula: “LA end-diastolic volume/LV end-diastolic volume”, assessed by CMR. The LA and LV volumes were measured with a match in the same end-diastolic phase, defined by mitral valve closure. Of note, LA end-diastolic and end-systolic volumes correspond respectively to the minimum left atrial volume index (LAVI_{min}) and the maximum left atrial volume index (LAVI_{max}) (Central Illustration). The intra- and inter-reader reproducibility of the LACI were assessed using a random sample size of 100 participants following a method published previously [8]. The LACI value is expressed as a percentage, and a higher LACI value indicates greater disproportionality between the LA and LV volumes at ventricular end-diastole, reflecting greater impairment of left atrioventricular coupling. Moreover, the Δ LACI is defined by the annual difference in the LACI value measured at baseline at Exam 1 (LACI_{Baseline}) and the LACI value measured after 10 years at Exam 5, and the Δ LACI value is expressed as a percentage per year.

Statistical analyses

The participants’ characteristics at baseline and after 10 years are presented as means \pm standard deviations for continuous variables, and as counts and percentages for categorical variables (Table 1). Using boxplots to assess the relationship between the categorical variables LACI and Δ LACI, comparison tests were based on the Cochran-Armitage test for trends. We used multivariable linear regression to identify demographic data, traditional cardiovascular risk factors, inflammation biomarkers (interleukin 6, high sensitivity C-reactive protein), myocardial fibrosis variables (native T1 mapping, extracellular volume [ECV]) and cardiovascular biomarkers (high-sensitivity cardiac troponin T, N-terminal prohormone of B-type natriuretic peptide [NT-proBNP]) at baseline that were independently associated with LACI_{Baseline} and Δ LACI. In a series of three models, we introduced interaction terms between sociodemographic variables, significant cardiovascular risk factors and the LV mass-to-volume ratio (MVR) as a measure of LV remodelling and diastolic dysfunction, as follows: Model 1 (demographic): adjusted for age, sex, ethnicity, level of education and body mass index (BMI); Model 2 (demographic + cardiovascular risk factors): adjusted for the variables in Model 1 in addition to systolic blood pressure, diabetes mellitus, smoking status, low-density lipoprotein and high-density lipoprotein; Model 3 (demographic + cardiovascular risk factors + LV structure): adjusted for the variables in Model 2 in addition to the LV MVR assessed by CMR.

Multivariable regression coefficients (B) were reported for each analysis and R² coefficients for each variable. The correlation between LACI_{Baseline} or Δ LACI and the other

variables was assessed using Pearson’s correlation test for variables with a normal distribution, or Spearman’s correlation test for variables with a non-normal distribution. For the linear regression, the variables with a non-normal distribution underwent a logarithmic transformation. A two-tailed *P*-value < 0.05 was considered statistically significant. All data were analysed using R software, version 3.6.1 (R Project for Statistical Computing, Vienna, Austria).

Results

Study population

Among the 4859 MESA participants with baseline CMR studies including LA volume assessment, 2112 (43.5%) had at least two CMR examinations (baseline and after 10-year follow-up) with LA and LV data available (mean age 58.8 ± 9.1 years; 46.6% men). Among these, 42.8% were White, 24.6% were African American, 20.6% were Hispanic and 12.0% were Chinese. Among the 2112 participants, 36.0% had hypertension, with 29.5% on antihypertensive therapy, 11.4% were current smokers, 9.4% had diabetes mellitus and the mean BMI was 27.8 ± 5.0 kg/m². The characteristics of the study population at Exam 1 and Exam 5 (after a mean time of 9.5 ± 0.6 years) are presented in Table 1. The population characteristics of all eligible MESA participants at baseline are described in Table A.1. Of note, the eligible participants at baseline (*n* = 6814) were older and had a higher rate of hypertension, diabetes mellitus and current smoking than the participants in this current analysis (*n* = 2112).

LACI and annualized change in LACI

For the entire study population, the mean LACI_{Baseline} value was $16.4 \pm 7.5\%$, and at follow-up the mean LACI value measured after 10 years at Exam 5 was $25.9 \pm 11.0\%$, with a mean Δ LACI of $1.1 \pm 1.0\%$ /year (Fig. A.1). Changes in LACI (Δ LACI) and individual LA and LV variables over 9.5 ± 0.6 years are shown in Table A.2. Regarding the evolution of LACI over 10 years, as stratified by the LACI_{Baseline} value, a lower value of LACI_{Baseline} was associated with a higher Δ LACI over 10 years (Fig. A.2). The intra- and inter-reader reproducibilities of the LACI were good, with intraclass correlation coefficients of 0.93 (95% confidence interval 0.90 to 0.96) and 0.81 (95% confidence interval 0.71 to 0.88), respectively [8].

Determinants of LACI and Δ LACI

Using multivariable linear regression analysis, the variables independently associated with LACI were age, African American ethnicity, BMI, diabetes mellitus and LV MVR. Similarly, the independent determinants of Δ LACI were age, male sex, high level of education versus other and LV MVR (Table 2).

Age in relation to LACI and Δ LACI

Association between age and LACI or Δ LACI is depicted in Fig. 2. Using four age categories, there was a positive association between age at baseline and the LACI_{Baseline} value, with 14.9%, 16.3%, 18.0% and 19.8% for participants aged 45–54 years, 55–64 years, 65–74 years and 75–84

Table 1 Characteristics of participants at Exam 1 and Exam 5.

Variables	Exam 1 (baseline)	Exam 5, 9.5 ± 0.6 years after baseline
	(n = 2112)	(n = 2112)
Age (years)	58.8 ± 9.1	68.3 ± 9.0
Male sex	985 (46.6)	985 (46.6)
Ethnicity		
White	43	43
Chinese American	12	12
African American	25	25
Hispanic	21	21
Education		
< High school	443 (21.0)	443 (21.0)
High school, technical school or associate degree	1062 (50.3)	1062 (50.3)
College, graduate or professional school	607 (28.7)	607 (28.7)
Hypertension	761 (36.0)	1166 (55.2)
Systolic blood pressure (mmHg)	123 ± 20	122 ± 20
Diastolic blood pressure (mmHg)	72 ± 10	69 ± 10
Hypertension medication	624 (29.5)	1064 (50.4)
BMI (kg/m ²)	27.8 ± 5.0	28.1 ± 5.1
Glycaemic status		
Normal	1684 (79.7)	1325 (62.7)
Impaired fasting glucose	229 (10.8)	433 (20.5)
Diabetes mellitus	199 (9.4)	354 (16.8)
Smoking status		
Never	1108 (52.5)	980 (46.4)
Former	764 (36.2)	972 (46.0)
Current	240 (11.4)	160 (7.6)
Total cholesterol (mg/dL)	195 ± 34	185 ± 36.2
HDL cholesterol (mg/dL)	52 ± 15	56 ± 16
Lipid-lowering medication	296 (14.0)	756 (35.8)
Glomerular filtration rate ^a (mL/min)	80 ± 15	81 ± 17
NT-proBNP (pg/mL)	69 ± 101	–
hs-cTnT (pg/mL)	6.8 ± 8.3	–
IL-6 (pg/mL)	1.7 ± 1.4	–
hsCRP (mg/L)	4.3 ± 6.2	–
Heart rate (beats/min)	62 ± 9	64 ± 10
LA variables		
LAVI _{min} (mL/m ²)	11.6 ± 5.7	15.9 ± 7.2
LAVI _{max} (mL/m ²)	29.5 ± 9.0	34.9 ± 10.7
LAVI _{preA} (mL/m ²)	21.8 ± 7.3	26.7 ± 9.0
Peak LA strain (%)	37.3 ± 11.0	32.0 ± 13.5
LV variables		
LV EDVi (mL/m ²)	70.1 ± 11.8	64.2 ± 13.3
LVEF (%)	62.6 ± 5.6	62.1 ± 7.0
LV mass index (g/m ²)	64.9 ± 11.6	65.9 ± 13.7
LV MVR (g/mL)	0.93 ± 0.17	1.04 ± 0.22
Native T1 mapping (ms)	978 ± 43	–
ECV (%)	27.0 ± 3.0	–
LACI (%)	16.4 ± 7.5	25.9 ± 11.0

Data are expressed as mean ± standard deviation, number (%) or %. BMI: body mass index; ECV: extracellular volume; EDVi: end-diastolic volume index; HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein; hs-cTnT: high-sensitivity cardiac troponin T; IL-6: interleukin-6; LA: left atrial; LACI: left atrioventricular coupling index; LAVI_{max}: maximum left atrial volume index; LAVI_{min}: minimum left atrial volume index; LAVI_{preA}: left atrial volume index before atrial contraction; LV: left ventricular; LVEF: left ventricular ejection fraction; MVR: mass-to-volume ratio; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide.

^a Calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

Table 2 Multivariable regression models for association of clinical, biological and cardiac magnetic resonance variables with left atrioventricular coupling index or annualized change in left atrioventricular coupling index over 10 years (regression coefficients B and P value).

Variables measured at baseline	LACI _{Baseline} ^a		ΔLACI ^b	
	Coefficient B (95% CI)	P	Coefficient B (95% CI)	P
Age, per 5 years	1.47 (1.09 to 1.85)	<0.001	0.3 (0.2 to 0.4)	<0.001
Male sex	0.50 (−0.22 to 1.22)	0.17	−0.1 (−0.3 to −0.2)	0.015
Ethnicity (African American versus other)	1.48 (0.72 to 2.24)	<0.001	0.0 (−0.1 to 0.1)	0.94
BMI, per kg/m ²	0.24 (0.17 to 0.31)	<0.001	0.2 (−0.1 to 0.4)	0.09
High level of education versus other	0.22 (−0.79 to 1.23)	0.67	−0.2 (−0.3 to −0.1)	0.013
Systolic blood pressure, per mmHg	−0.10 (−0.21 to 0.10)	0.60	0.0 (−0.1 to 0.1)	0.56
Diabetes mellitus	1.75 (0.65 to 2.86)	<0.001	0.1 (−0.1 to 0.3)	0.11
Current smoker versus non-smoker	−0.82 (−1.81 to 0.18)	0.11	0.1 (−0.1 to 0.4)	0.06
LDL cholesterol, per mg/dL	−0.10 (−0.12 to 0.10)	0.77	−0.0 (−0.1 to 0.1)	0.60
HDL cholesterol, per mg/dL	−0.22 (−0.10 to 0.40)	0.17	0.0 (−0.1 to 0.1)	0.08
LV MVR, per unit	4.15 (2.05 to 6.26)	<0.001	0.4 (0.1 to 0.7)	0.005

BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; LACI: left atrioventricular coupling index; ΔLACI: annualized change in left atrioventricular coupling index over 10 years; LDL, low-density lipoprotein; LV: left ventricular; MVR: mass-to-volume ratio.

^a Model 3 (demographic + cardiovascular risk factors + LV remodelling) adjusted for: age, sex, ethnicity, high level of education (≥ college, graduate or professional school), BMI, systolic blood pressure, diabetes mellitus, smoking status, LDL, HDL and LV MVR assessed by cardiac magnetic resonance.

^b Model adjusted for: the variables in Model 3 in addition to LACI_{Baseline}.

Table 3 Regression models for association of left atrioventricular coupling index or annualized change in left atrioventricular coupling index over 10 years with age, according to sex (regression coefficients B and P value).

		Model 1 ^a		Model 2 ^b		Model 3 ^c	
		Coefficient B (95% CI)	P	Coefficient B (95% CI)	P	Coefficient B (95% CI)	P
Association of LACI _{Baseline} with age (% per 5 years of age)	Women	1.65 (1.20 to 2.25)	< 0.001	1.43 (1.12 to 1.89)	<0.001	1.22 (1.08 to 1.77)	0.001
	Men	1.60 (1.11 to 2.23)	<0.001	1.37 (1.07 to 1.67)	0.002	1.18 (1.04 to 1.60)	0.008
Association of ΔLACI with age (%/year per 5 years of age)	Women	0.25 (0.19 to 0.42)	<0.001	0.23 (0.16 to 0.39)	<0.001	0.17 (0.11 to 0.25)	0.001
	Men	0.22 (0.16 to 0.41)	<0.001	0.21 (0.14 to 0.38)	<0.001	0.14 (0.08 to 0.23)	0.001

CI: confidence interval; LACI_{Baseline}: left atrioventricular coupling index at baseline; ΔLACI: annualized change in left atrioventricular coupling index over 10 years.

^a Model 1 (demographic) adjusted for: age, sex, ethnicity, level of education and body mass index.

^b Model 2 (demographic + cardiovascular risk factors) adjusted for: the variables in Model 1 in addition to systolic blood pressure, diabetes mellitus, smoking status, low-density lipoprotein and high-density lipoprotein.

^c Model 3 (demographic + cardiovascular risk factors + left ventricular remodelling) adjusted for: the variables in Model 2 in addition to left ventricular mass-to-volume ratio assessed by cardiac magnetic resonance.

years, respectively (P trend < 0.001; Table A.3). Consistent with this, the ΔLACI over 10 years increased significantly with the age categories at baseline (P trend < 0.001, Table A.3). In the multivariable analysis, after adjustments for all covariates in Model 3, there was a linear relationship between age at baseline and the LACI_{Baseline}

value (adjusted $R^2 = 0.10$, slope = 0.16; $P < 0.001$) and ΔLACI (adjusted $R^2 = 0.15$, slope = 0.008; $P < 0.001$). Both associations were constant, regardless of the sex of participants (Fig. A.3). For the relationship of age with LACI_{Baseline} and ΔLACI, Table 3 shows the regression coefficients (B) derived from the multivariable linear regression analyses.

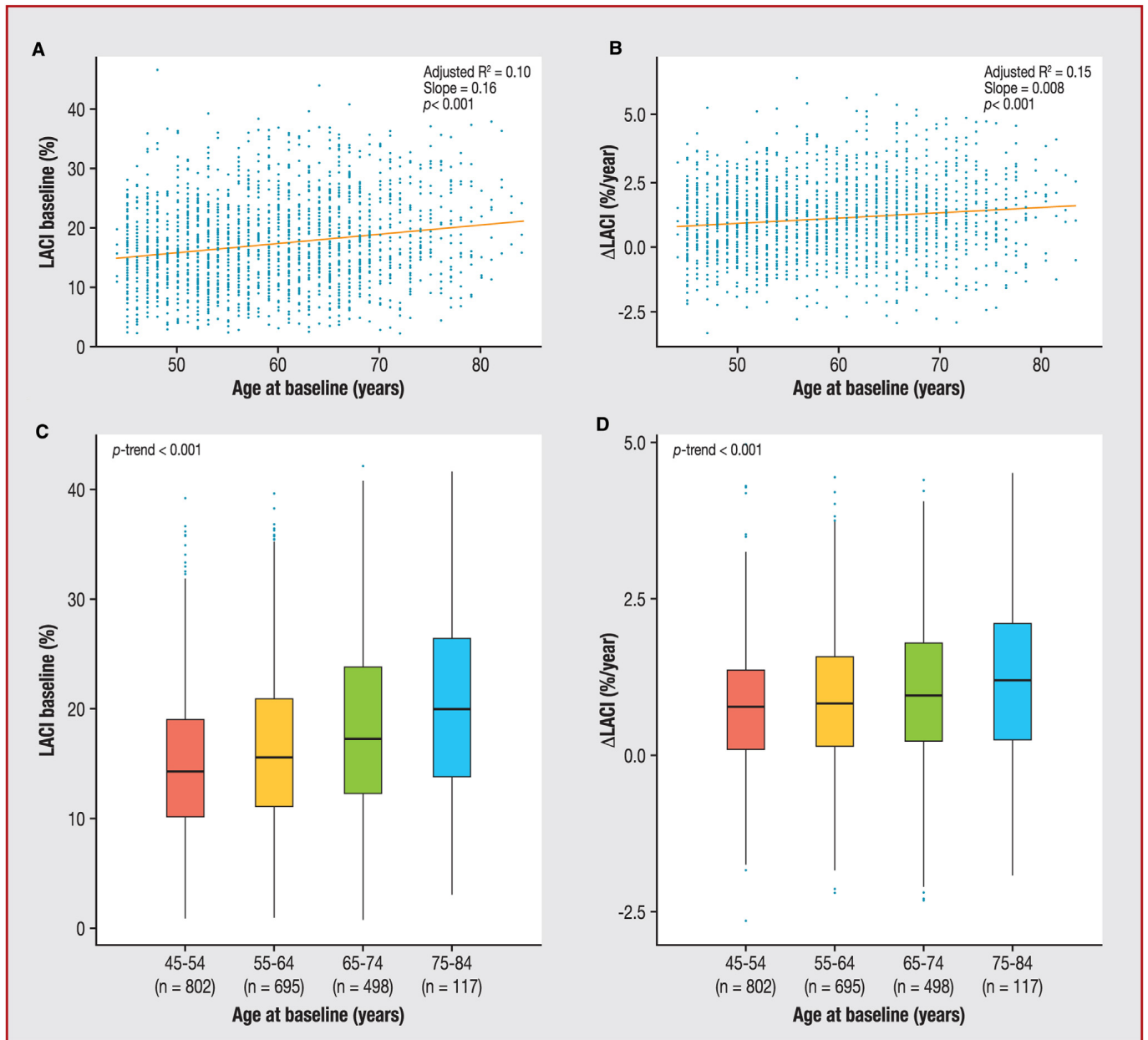


Figure 2. Association between age and left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (Δ LACI). A–B. Regression plot between age and the baseline LACI value ($LACI_{\text{Baseline}}$) (A) and Δ LACI (B) in all cohorts after adjustments for all covariates in Model 3. C–D. Mean $LACI_{\text{Baseline}}$ value (C) and Δ LACI (D) in each age category; the bottom and top of each box are the first and third quartiles, and the band inside each box is the median.

$LACI_{\text{Baseline}}$ and Δ LACI were positively associated with age in all adjusted models, regardless of sex.

Sex in relation to LACI and Δ LACI

Although there was no significant difference in the $LACI_{\text{Baseline}}$ value between women and men (16.2 ± 7.6 vs $16.6 \pm 7.4\%$, respectively; $P=0.19$), Δ LACI was higher in women than in men (1.0 ± 1.1 vs $0.8 \pm 1.1\%$ /year; $P<0.001$) (Table A.3). In addition, women had a higher Δ LACI than men in all age categories (Fig. 3). In the multivariable linear regression analysis, there was no relationship between sex and the $LACI_{\text{Baseline}}$ value ($P=0.17$), but male sex was

inversely related to Δ LACI (multivariable regression coefficient B: -0.10 per year; $P=0.015$) (Table 2).

Ethnicity in relation to LACI and Δ LACI

$LACI_{\text{Baseline}}$ and Δ LACI values differed by race/ethnicity ($P<0.001$) (Table A.3). African Americans had the highest $LACI_{\text{Baseline}}$ value ($18.0 \pm 7.7\%$), whereas Chinese participants had the lowest $LACI_{\text{Baseline}}$ ($13.8 \pm 6.4\%$; $P<0.001$) (Fig. A.4).

Although there was no significant difference in the Δ LACI value between African Americans and non-African Americans (0.9 ± 1.1 vs. $0.9 \pm 1.1\%$ /year; $P=0.95$), the $LACI_{\text{Baseline}}$ was higher in African Americans than in non-African Americans (18.0 ± 7.7 vs. $15.8 \pm 7.4\%$; $P<0.001$) (Table A.3). Assessing the age interaction, African Americans aged

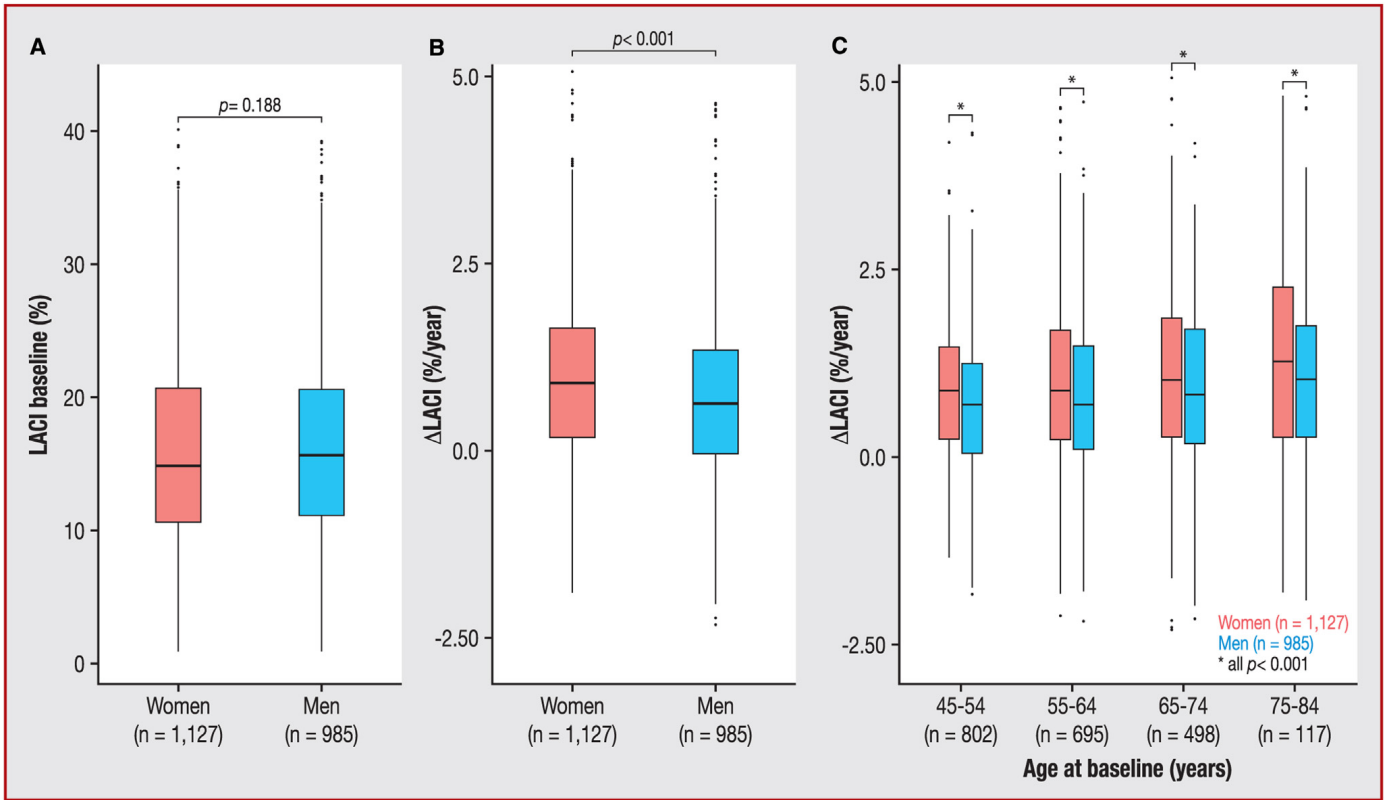


Figure 3. Association between sex and left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (Δ LACI). A–B. Boxplot distribution of the baseline LACI value ($LACI_{Baseline}$) (A) and Δ LACI (B) stratified by sex. C. The mean Δ LACI value in each age category at baseline is stratified according to sex. The bottom and top of each box are the first and third quartiles, and the band inside each box is the median.

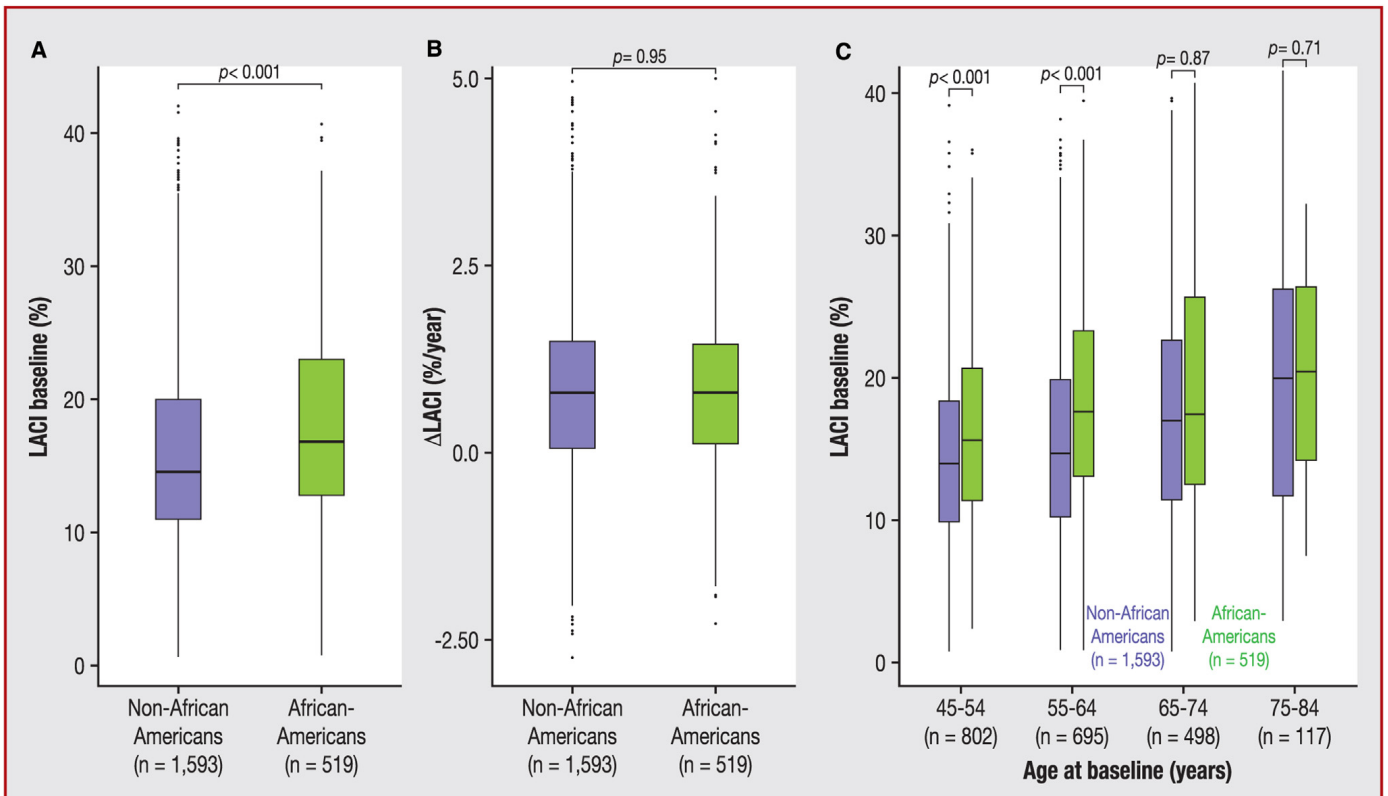


Figure 4. Association between ethnicity and left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (Δ LACI). A–B. Boxplot distribution of the baseline LACI value ($LACI_{Baseline}$) (A) and Δ LACI (B) stratified by ethnicity (African American versus non-African American). C. The mean $LACI_{Baseline}$ value in each age category at baseline is stratified according to ethnicity. The bottom and top of each box are the first and third quartiles, and the band inside each box is the second quartile (the median).

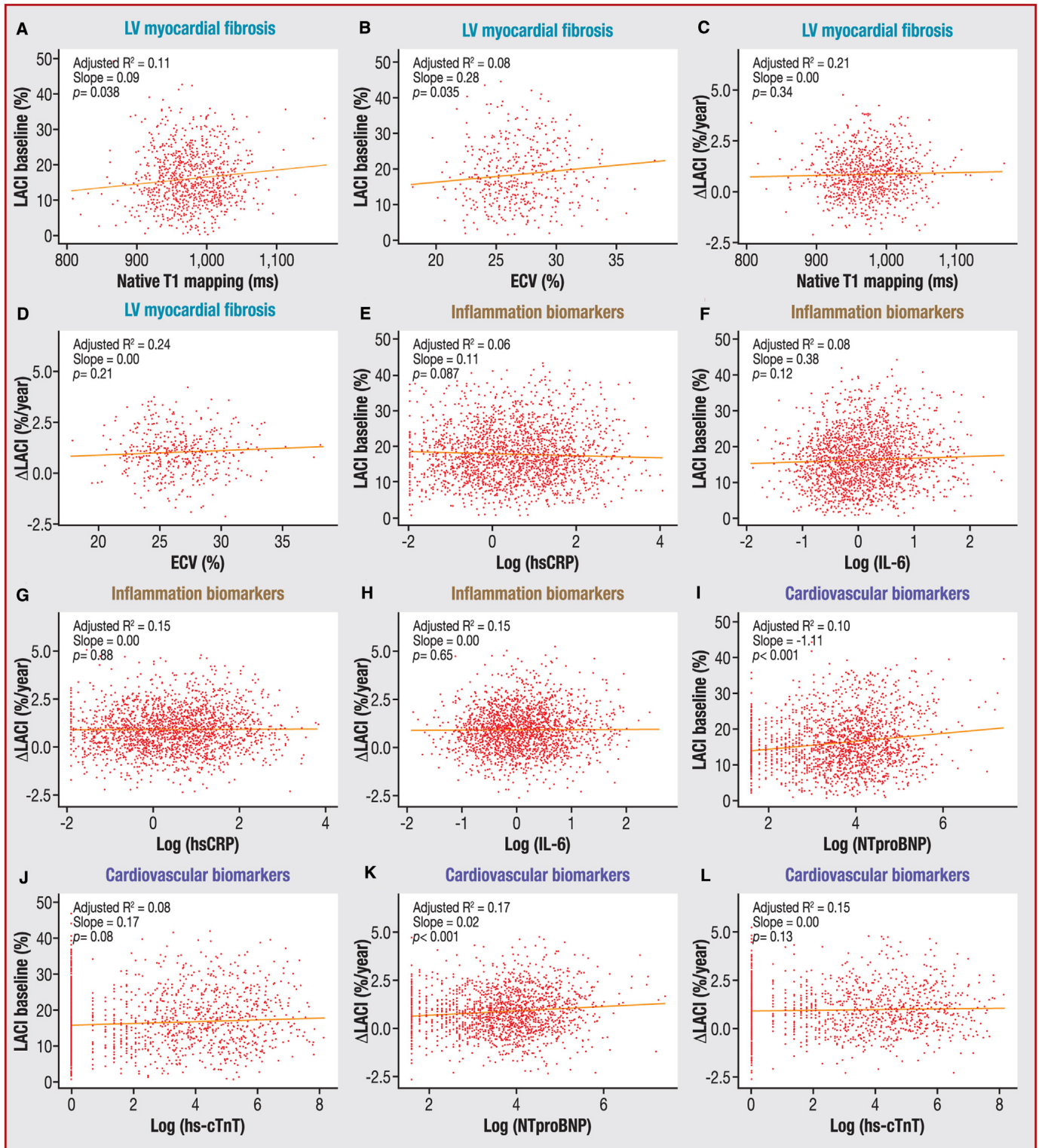


Figure 5. Association between left atrioventricular coupling index (LACI) or annualized change in LACI over 10 years (Δ LACI) and left ventricular (LV) myocardial fibrosis, inflammation and cardiovascular biomarkers at baseline. A–L. After adjustments for all covariates in Model 3, a regression plot between LACI at baseline ($LACI_{\text{baseline}}$) and LV myocardial fibrosis markers (native T1 mapping, A; extracellular volume [ECV], B), inflammation biomarkers (high-sensitivity C-reactive protein [hsCRP], E; interleukin-6 [IL-6], F) and cardiovascular biomarkers (N-terminal prohormone of B-type natriuretic peptide [NT-proBNP], I; high-sensitivity cardiac troponin T [hs-cTnT], J); after adjustments for all covariates in Model 3, a regression plot between Δ LACI and LV myocardial fibrosis markers (native T1 mapping, C; ECV, D), inflammation biomarkers (hsCRP, E; IL-6, H) and cardiovascular biomarkers (NT-proBNP, K; hs-cTnT, L).

45–64 years had a higher $LACI_{\text{baseline}}$ value than non-African Americans ($17.8 \pm 7.8\%$ vs. $15.2 \pm 7.9\%$; $P < 0.001$), whereas after age ≥ 65 years, there was no difference between

African Americans and non-African Americans ($18.6 \pm 8.2\%$ vs. $18.4 \pm 8.1\%$; $P = 0.72$) (Fig. 4). In the multivariable linear regression analysis, there was an independent relationship

between African American ethnicity and the $LACI_{\text{Baseline}}$ value (multivariable regression coefficient B: 1.48; $P < 0.001$), but there was no relationship between ethnicity and $\Delta LACI$ ($P = 0.94$) (Table 2).

Cardiovascular risk factors at baseline in relation to $LACI$ and $\Delta LACI$

In the multivariable linear regression analysis, there was a relationship between diabetes mellitus and $LACI_{\text{Baseline}}$ (coefficient B: 1.75%; $P < 0.001$) and BMI and $LACI_{\text{Baseline}}$ (coefficient B: 0.24% per increment of BMI; $P < 0.001$), which was not the case for $\Delta LACI$ ($P = 0.09$) (Table 2). In addition, there was no relationship between hypertension, smoking status, low-density lipoprotein cholesterol or high-density lipoprotein cholesterol and $LACI_{\text{Baseline}}$ or $\Delta LACI$.

Myocardial fibrosis, inflammation and cardiovascular biomarkers at baseline in relation to $LACI$ and $\Delta LACI$

In the multivariable analysis, after adjustments for all covariates in Model 3, both native T1 value and ECV as LV myocardial fibrosis markers at baseline were independently associated with the $LACI_{\text{Baseline}}$ value [adjusted $R^2 = 0.11$, slope = 0.09 ($P = 0.038$) and adjusted $R^2 = 0.08$, slope = 0.28 ($P = 0.035$), respectively], but not with $\Delta LACI$. In addition, NT-proBNP concentrations were also independently associated with both $LACI_{\text{Baseline}}$ and $\Delta LACI$ [adjusted $R^2 = 0.10$, slope = -1.11 ($P < 0.001$) and adjusted $R^2 = 0.17$, slope = 0.02 ($P < 0.001$), respectively]. There was no association between baseline high-sensitivity C-reactive protein or interleukin 6 (as inflammation biomarkers) or baseline high-sensitivity cardiac troponin T and $LACI_{\text{Baseline}}$ or $\Delta LACI$ (Fig. 5).

Relationship of baseline LA or LV variables with $LACI$ and $\Delta LACI$

In the multivariable analysis, after adjustments for all covariates in Model 3, $LAVI_{\text{min}}$, $LAVI_{\text{max}}$, LV mass and LV MVR were positively associated with the $LACI_{\text{Baseline}}$ value, but peak LA strain was inversely related to the $LACI_{\text{Baseline}}$ value (all $P < 0.001$) (Fig. A.5).

Discussion

In a population of participants free of clinical CVD, this study has emphasized important findings regarding the determinants of the $LACI$ at baseline and its 10-year annual change ($\Delta LACI$) as markers of LA/LV coupling: (1) an increase in age was independently associated with an increase in both $LACI_{\text{Baseline}}$ and $\Delta LACI$ after adjustment for all covariates; (2) although there was no difference in $LACI_{\text{Baseline}}$ between women and men, $\Delta LACI$ was higher in women than in men; (3) regarding the ethnicity of participants, African Americans had the highest $LACI_{\text{Baseline}}$ value, whereas Chinese participants had the lowest; (4) diabetes mellitus and higher BMI were independently associated with $LACI_{\text{Baseline}}$; (5) $LACI_{\text{Baseline}}$ was independently associated with LV myocardial fibrosis markers and NT-proBNP concentration, but there

was no association between $LACI_{\text{Baseline}}$ and inflammation biomarkers or high-sensitivity cardiac troponin T.

The $LACI$ identifies an earlier stage of LA remodelling associated with impaired LV compliance when compared with individual LA variables, and has a higher prognostic value for predicting cardiovascular events after adjustment for traditional risk factors [8–10]. With increased age, there are changes in LA volume or function and LV filling [16]. However, the data are insufficient for us to understand whether these age-dependent changes in LA volume and function result from isolated LA physiological alterations or from impaired LA/LV coupling. In the current study, aging was one of the most important determinants of $LACI$ and its evolution. Indeed, age was strongly associated with both $LACI_{\text{Baseline}}$ and $\Delta LACI$, regardless of the sex of participants. Moreover, this age-related degradation of LA/LV coupling over 10 years ($\Delta LACI$) was more accelerated for older participants. The hypothesis of the impact of aging on LA/LV coupling has already been raised by a CMR study performed in 40 healthy individuals to investigate the effects of aging on LA/LV coupling and LV filling [17]. The oldest individuals had larger LA and smaller LV volumes, with larger LA/LV end-diastolic volume ratios.

Although there was no difference between women and men for the $LACI$ value at baseline, the degradation of the LA/LV coupling over 10 years, assessed by $\Delta LACI$, was more accelerated for women than men, regardless of age. To explain these findings, we can hypothesize that menopausal status and sex hormone concentrations could play a role in LA/LV coupling and modulation of the $LACI$ value in women [18]. A recent study assessing 14,550 post-menopausal women from the UK Biobank indicated that menopause was independently associated with a lower LV end-diastolic volume [19]. Another recent study emphasized the significant relationship between sex hormone concentrations and changes in LV structure [20]. Beyond these consequences for LV remodelling, some studies have also suggested an effect of menopause on LA remodelling [21].

This study suggests that the $LACI$ value was different depending on the ethnicity of the participants. By stratifying the population as White, African American, Hispanic and Chinese, African Americans had the highest $LACI_{\text{Baseline}}$ values. This higher $LACI$ value among African Americans led us to conduct a second analysis comparing African Americans and non-African Americans. Although there was no significant difference in $\Delta LACI$ between African Americans and non-African Americans, $LACI_{\text{Baseline}}$ was higher in African Americans than in non-African Americans. In the subgroup analysis investigating the age interaction, African Americans aged 45–64 years had a higher $LACI_{\text{Baseline}}$ value than non-African Americans, whereas in participants aged ≥ 65 years, there was no difference between African Americans and non-Africans. All these results suggest that there was worse LA/LV coupling (higher $LACI$ value) in young African Americans than in non-African Americans, but after the age of 65 years, the age-related degradation of the LA/LV coupling was similar in both populations. These findings are in line with studies reporting that African American participants present a higher risk of CVD (hazard ratio of 3 for cardiovascular death).

Regarding cardiovascular risk factors, only diabetes and higher BMI were associated with the $LACI$ value at baseline.

These findings are consistent with studies reporting that LV end-diastolic volume decreased and LA volumes increased in patients with diabetes [22]. Therefore, recent reports suggest that LA/LV coupling is an important predictor of CVD in patients with diabetes [23]. Consistent with this, a recent study has shown a mechanical impact of diabetes on this coupling through a decrease in global atrioventricular strain using echocardiography [24].

Our study also describes the independent association between native T1 and ECV values as markers of LV myocardial fibrosis and the LACI value at baseline. These findings reinforce the hypothesis of a mechanical phenomenon involving LA/LV coupling and myocardial fibrosis. In line with reports indicating that ECV and native T1 values are correlated with NT-proBNP concentrations [25], this study showed a significant correlation between LACI and NT-proBNP concentrations. Whereas chronic inflammation and its biomarkers (high-sensitivity C-reactive protein and interleukin 6) may have roles in the genesis and prediction of CVD [26], there was no association between inflammation biomarkers and LACI values in this study. Although this study provides several hypotheses about the determinants of LACI, its 10-year annual change and factors involved in LA/LV coupling, future studies should be conducted to confirm these results.

Beyond the determinants of LACI explored in this study, several studies performed by our working group have shown the incremental prognostic value of LACI beyond any separately assessed LA or LV variable in predicting the risk of incident heart failure or atrial fibrillation [8–10]. All these results suggest a potential role for LACI as a screening tool to improve our management of patients in primary prevention.

Study limitations

First, Δ LACI was averaged across 10 years, thus assuming linearity over time. This method may not have fully captured the variation in year-to-year measurements, which provides additional precedence for further investigation. Second, the exclusion of patients who presented a cardiovascular event between the two CMR examinations limits the assessment of the clinical value of LACI in daily practice. However, the exclusion of these patients avoided potential confounding factors in the mechanistic description of left atrioventricular coupling in patients without CVD. Therefore, the results of this study cannot be applied to patients with severe LA or LV enlargement. In addition, there was a significant selection bias related to the exclusion of a high proportion of patients with only one CMR examination. Third, the current study identified the determinants of reduced LACI rather than LACI itself. Thus, further physiology studies are needed to investigate the determinants of left atrioventricular coupling more thoroughly itself. Fourth, we used two-dimensional instead of three-dimensional methods to measure LA volumes, which may have underestimated the true volumes by 11.5–20% [27]. However, this method has been widely used and validated in clinical studies [13,16]. Fifth, one limitation of the native T1 and ECV CMR methods is that these indices may vary depending on the magnetic resonance imaging technique, field strength, gadolinium contrast agent and dosage used for the T1 measurement [2]. Sixth, the study population was at very low risk of cardiovascular events, with an

event rate of only 4.6% after 10 years of follow-up. Finally, the effects of age on the cardiovascular system are probably inseparable from multifactorial events accumulated over a lifetime, including both known and unknown factors that affect the myocardium.

Conclusions

In a large multi-ethnic population free of clinical CVD, we identified some independent determinants of a LACI and its 10-year annual change (Δ LACI), namely age, sex, ethnicity, diabetes and a higher BMI. In addition, LACI was independently associated with LV myocardial fibrosis markers and NT-proBNP concentrations, but was not associated with inflammation biomarkers.

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Disclosure of interest

The authors declare that they have no competing interest.

Online Supplement. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.acvd.2022.04.011>.

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Partie 4 :

Altération du couplage auriculo-ventriculaire gauche liée à la ménopause

Prognostic value of a left atrioventricular coupling index in pre- and post-menopausal women from the Multi-Ethnic Study of Atherosclerosis

Pezel, T ; Michos ED, Varadarajan V, Shabani M, Venkatesh BA, Vaidya D, Kato Y, De Vasconcellos HD, Heckbert SR, Wu CO, Post WS, Bluemke DA, Allison MA, Henry P, Lima JAC.

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Dans la continuité de l'étude n°2 qui avait montré des différences importantes des valeurs de l'indice de couplage auriculo-ventriculaire gauche (LACI) et de son évolution entre hommes et femmes, nous avons proposé cette nouvelle étude pour investiguer le rôle et la valeur pronostique de l'altération du couplage auriculo-ventriculaire gauche chez les femmes, notamment par rapport au statut ménopausique et aux hormones sexuelles.

Ainsi, l'objectif de cette troisième étude est d'évaluer la valeur pronostique d'un indice de couplage auriculo-ventriculaire gauche (LACI) chez les femmes en péri-ménopause sans antécédents de maladie cardiovasculaire. Chez toutes les femmes participant à l'étude MESA avec une IRM cardiovasculaire initiale, le LACI a été mesuré comme le rapport du volume télédiastolique LA au volume télédiastolique VG. Des modèles de Cox ont été utilisés pour évaluer l'association entre le LACI et les résultats de la fibrillation auriculaire, de

l'insuffisance cardiaque, de la mort de cause coronaire et des maladies cardiovasculaires graves.

Parmi les 2 087 femmes participantes (61 ± 10 ans), 485 événements cardiovasculaires sont survenus après un suivi moyen de $13,2 \pm 3,3$ ans. Un LACI plus élevé était indépendamment associé à la fibrillation auriculaire (HR 1,70 ; IC à 95 % [1,51–1,90]), l'insuffisance cardiaque (HR 1,62 ; IC à 95 % [1,33–1,97]), le décès par coronaropathie (HR 1,36 ; IC à 95 % [1,10–1,68]) et les maladies cardiovasculaires graves (HR 1,30 ; IC à 95 % [1,13–1,51], tous $p < 0,001$). En utilisant les modèles ajustés, le LACI a montré une amélioration significative de la discrimination et de la reclassification des modèles par rapport aux modèles traditionnels pour prédire : la fibrillation auriculaire (statistique C : 0,82 contre 0,79 ; NRI = 0,325 ; IDI = 0,036), l'insuffisance cardiaque (statistique C : 0,84 contre 0,81 ; NRI = 0,571 ; IDI = 0,023), le décès de cause coronaire (statistique C : 0,87 contre 0,85 ; NRI = 0,506 ; IDI = 0,012), les maladies cardiovasculaires (statistique C : 0,78 contre 0,76 ; NRI = 0,229 ; IDI = 0,012). La valeur pronostique du LACI avait une meilleure discrimination et reclassification que n'importe quel paramètre de l'oreillette gauche ou du ventricule gauche évalué séparément.

En résumé, cette troisième étude s'est concentrée sur une vaste population multiethnique de femmes pré- et post-ménopausées âgées de 45 à 84 ans qui n'avaient pas de maladie cardiovasculaire clinique au départ. Les participantes ont été suivies pendant plus de 13 ans. Les principaux résultats étaient les suivants :

- Le LACI a montré la plus grande association avec l'incidence de fibrillation auriculaire, d'insuffisance cardiaque, de décès de cause coronaire et de maladies cardiovasculaires graves, améliorant la discrimination du modèle et la reclassification du risque

d'événement cardiovasculaire au-dessus du statut ménopausique, des facteurs de risque cardiovasculaire traditionnels et du dosage des hormones sexuelles ;

- La valeur pronostique du LACI était homogène chez les femmes pré-ménopausées et post-ménopausées ;
- Les femmes post-ménopausées avaient une fonction auriculo-ventriculaire gauche moins bonne, définie par une valeur LACI plus élevée, que les femmes pré-ménopausées ;
- Les femmes post-ménopausées utilisant un traitement hormonal substitutif avaient une meilleure fonction auriculo-ventriculaire gauche, définie par une valeur LACI inférieure, que les femmes post-ménopausées n'utilisant pas de traitement hormonal substitutif ;
- Le LACI était positivement associé aux niveaux de testostérone totale et de DHEA, mais inversement associé au niveau d'estradiol.

À notre connaissance, la valeur pronostique d'un indice de couplage auriculo-ventriculaire gauche chez les femmes pré- et post-ménopausées et l'association entre le LACI et les niveaux d'hormones sexuelles n'avaient pas été bien établies auparavant.



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Prognostic value of a left atrioventricular coupling index in pre- and post-menopausal women from the Multi-Ethnic Study of Atherosclerosis

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Background: Sex hormones associated with both the left atrial (LA) and left ventricular (LV) structures in women, but the association of menopause status with left atrioventricular coupling is not established.

Aim: To assess the prognostic value of a left atrioventricular coupling index (LACI) in peri-menopausal women without a history of cardiovascular disease (CVD).

Materials and methods: In all women participating in MESA study with baseline cardiovascular MRI, the LACI was measured as the ratio of the LA end-diastolic volume to the LV end-diastolic volume. Cox models were used to assess the association between the LACI and the outcomes of atrial fibrillation (AF), heart failure (HF), coronary heart disease (CHD) death, and hard CVD.

Results: Among the 2,087 women participants (61 ± 10 years), 485 cardiovascular events occurred (mean follow-up: 13.2 ± 3.3 years). A higher LACI was independently associated with AF (HR 1.70; 95%CI [1.51–1.90]), HF (HR 1.62; [1.33–1.97]), CHD death (HR 1.36; [1.10–1.68]), and hard CVD (HR 1.30; [1.13–1.51], all $p < 0.001$). Adjusted models with the LACI showed significant improvement in model discrimination and reclassification when compared to traditional models to predict: incident AF (C-statistic: 0.82 vs. 0.79; NRI = 0.325; IDI = 0.036), HF (C-statistic: 0.84 vs. 0.81; NRI = 0.571; IDI = 0.023), CHD death (C-statistic: 0.87 vs. 0.85; NRI = 0.506; IDI = 0.012),

hard CVD (C-statistic: 0.78 vs. 0.76; NRI = 0.229; IDI = 0.012). The prognostic value of the LACI had a better discrimination and reclassification than individual LA or LV parameters.

Conclusion: In a multi-ethnic population of pre- and post-menopausal women, the LACI is an independent predictor of HF, AF, CHD death, and hard CVD.

Clinical trial registration: [<https://clinicaltrials.gov/>], identifier [NCT00005487].

KEYWORDS

Multi-Ethnic Study of Atherosclerosis (MESA), menopause, left atrioventricular coupling, cardiovascular magnetic resonance, prognosis, sex hormones (SH), cardiovascular events (CVE)

Introduction

Although the risk of cardiovascular disease (CVD) is much lower in women than in men until 50 years of age, it rises dramatically after menopause (1, 2). This higher rate of cardiovascular events in peri- and post-menopausal women contributes significantly to morbi-mortality rates among women worldwide (3, 4). It has been hypothesized that the increased CVD risk in peri-menopausal women is due to lower levels of endogenous estrogens and higher levels of endogenous androgens during and after the menopausal transition (1, 5). In line with this hypothesis, a study from the Multi-Ethnic Study of Atherosclerosis (MESA), which assessed 2,834 post-menopausal women, recently showed that a more androgenic sex hormone profile was associated with women's increased CVD risk later in life, including coronary heart disease (CHD), and incident heart failure (HF) (6). Another study recently provided evidence of a significant relationship between post-menopausal hormone levels and changes in left ventricular (LV) structure (7).

The protective role of estrogen on the cardiovascular system has already been described, along with the mediating mechanisms, such as fibrosis, oxidative stress, vascular function, and ventricular remodeling (8). Regarding this last point, a very recent study described the modifications caused by LV remodeling due to menopause using cardiovascular magnetic resonance (CMR) in 14,550 post-menopausal women (9). In this study, menopause was independently associated with smaller

LV end-diastolic volume and smaller LV stroke volume (9). Beyond these effects on LV remodeling, some studies have also suggested a potential repercussion of menopause on left atrial (LA) remodeling (10, 11). Therefore, we can assume that hormone levels could cause LA remodeling and functional change in peri- and post-menopausal women.

Given that sex hormone levels may cause both LA and LV remodeling, it is relevant to assess the potential consequences of the menopausal transition on left atrioventricular coupling. Indeed, the left atrium and ventricle interact throughout the cardiac cycle. During diastole, the LA and LV are directly connected, and in the absence of valvular disease, their function is tightly coupled (12). However, there is a paucity of literature on the ability of atrioventricular coupled indexes to predict outcomes with very limited sample sizes (13, 14). Recently, our working group demonstrated the prognostic value of a novel left atrioventricular coupling index (LACI) defined by the ratio of the LA end-diastolic volume divided by the LV end-diastolic volume using CMR (15). Those prior MESA results, conducted in both men and women, suggested that an increase in LACI is associated with cardiovascular outcomes. Using a longitudinal analysis, our team has also shown the incremental prognostic value of annualized change in LACI over 10 years (?LACI), along with traditional risk factors, which had a better prognostic value than individual changes in LA or LV parameters measured separately to predict incident HF (16), and incident atrial fibrillation (AF) (17). More recently, Meucci et al. showed its strong prognostic value for incident AF in patients with hypertrophic cardiomyopathy (18). All these findings support the physiological concept of left atrioventricular coupling by this LA/LV coupling index, which has a better prognostic value than individual LA or LV parameters measured separately (19). Despite peri- and post-menopausal women presenting a higher rate of cardiovascular events (1, 5), the potential role of the

Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CMR, cardiovascular magnetic resonance; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; HF, heart failure; HT, hormone therapy; IDI, integrative discrimination index; LA, left atrial; LACI, left atrioventricular coupling index; LV, left ventricular; LVEF, left ventricular ejection fraction; MESA, Multi-Ethnic Study of Atherosclerosis; NRI, net reclassification improvement; SHBG, sex hormone binding globulin.

menopause transition on left atrioventricular coupling in this population is not well established.

Therefore, we hypothesized that the menopausal transition plays a potential role through endogenous sex hormones in left atrioventricular coupling. Hence, we investigated the relationship between the LACI and the menopausal status and sex hormone levels, and then evaluated the prognostic value of the LACI to predict the occurrence of cardiovascular events in pre- and post-menopausal women in the MESA.

Materials and methods

Study population

The MESA is a prospective, community-based, multi-ethnic (consisting of self-reported White, African American, Chinese, and Hispanic race/ethnic groups) cohort study evaluating subclinical CVD and its progression to clinical CVD. The study design of the MESA has been described in detail previously (20). In summary, between 2000 and 2002 (Exam 1), 6,814 men and women aged 45–84 years and free of clinical CVD at enrollment were consecutively recruited from six US field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN). Participants with clinically significant CVD at baseline were excluded.

The current analysis included all women assessed by CMR at the baseline. Menopausal status was self-reported and corrected using information on age, self-reported hysterectomy, bilateral oophorectomy, and menopausal age. Baseline serum sex hormones were measured following a MESA protocol already described (7) and included estradiol, free and total testosterone (T), dehydroepiandrosterone (DHEA), and sex hormone binding globulin (SHBG). Total testosterone was divided by estradiol to calculate the total testosterone-to-estradiol ratio. The methodology of baseline characteristics collection is detailed in [Supplementary material 1](#). All participants provided written informed consent. All study protocols were approved by the institutional review boards of each participating field center.

A flowchart of the MESA population investigated in this study is depicted in [Figure 1](#).

Of the 2,248 women with CMR imaging data available that included LA volume assessment (Exam 1), 21 individuals had no follow-up for cardiovascular events, 77 had missing images or insufficient image quality to measure LA and LV volumes, and a further 63 had missing covariates. This resulted in a final cohort of 2,087 women available for analysis ([Figure 1](#)).

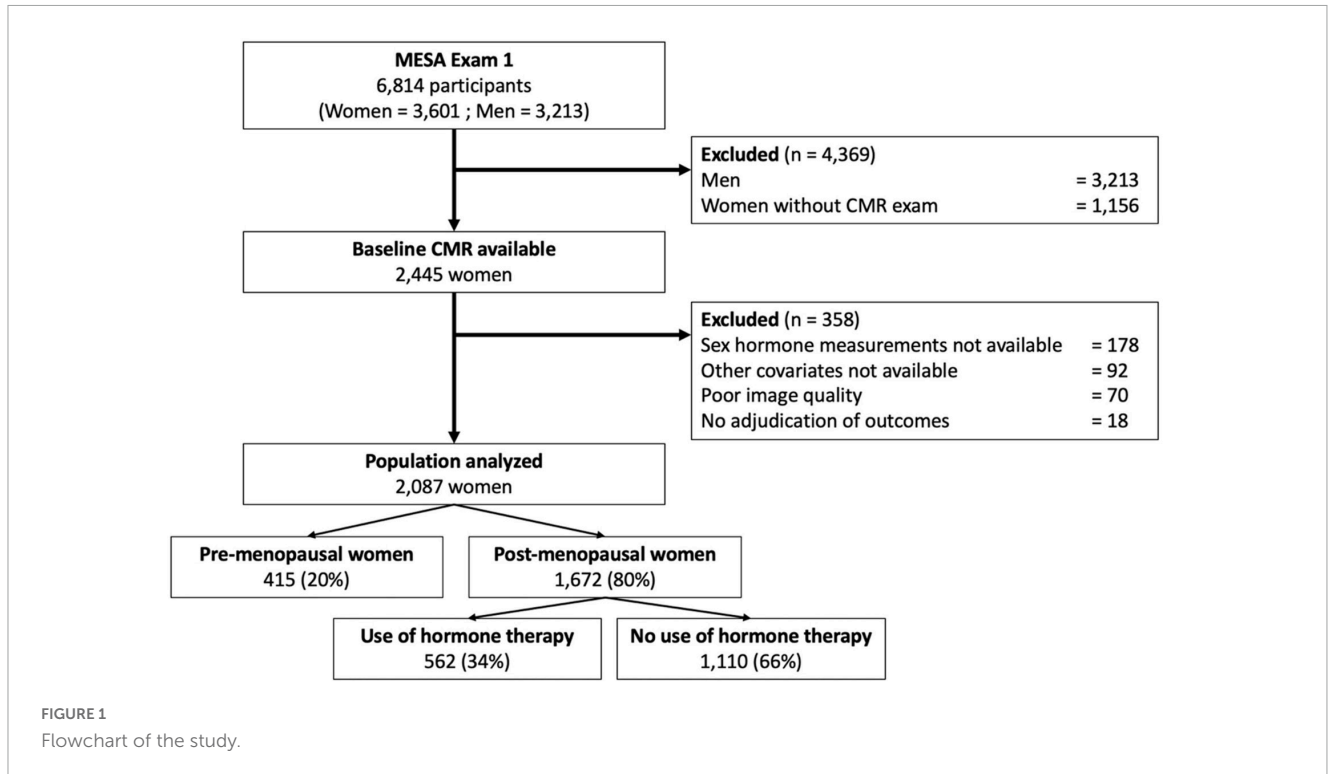
Cardiovascular magnetic resonance protocol and image analysis

The CMR protocol has been described in detail previously (21). Briefly, CMR was performed at six MESA field centers using 1.5-Tesla scanners ([Supplementary material 2](#)). Long-axis cine images were obtained from two- and four-chamber views using electrocardiogram-gated fast gradient-echo pulse sequences. A stack of short-axis cine images was acquired to encompass both ventricles, and LV end-diastolic volume was measured using cardiac image modeler software (CIM version-6.0, Auckland University, New Zealand). All cine images were acquired with a temporal resolution of ~50 ms. The complete CMR protocol as well as details of image analysis, data quality control, calculations for left ventricular ejection fraction (LVEF), LV mass and volumes, LA volumes, and reproducibility of these measurements have been published previously (21).

Multimodality tissue tracking software (MTT version-6.0, Toshiba Medical, Tokyo, Japan) was used to quantify LA volume and strain from two- and four-chamber cine CMR images ([Supplementary material 3](#)). This method has been validated previously, showing good to excellent intra- and inter-reader reproducibility, with intraclass correlation coefficient (ICC) of 0.88–0.98 ($p < 0.001$), and reasonable inter-study reproducibility, with ICC of 0.44–0.82 ($p < 0.05$ –0.001) (22–24). A single experienced operator blinded to the case status of the participant defined endocardial and epicardial borders of the LA at end-diastole. Using the marked points, the software created endocardial and epicardial borders, and then tracked LA tissue in subsequent frames.

Left atrioventricular coupling index

As recently described by our group (15), the LACI was defined as the ratio of the LA end-diastolic volume to the LV end-diastolic volume, as assessed using CMR. The LV volume was measured from the stack of short-axis cine images, while the LA volume was measured from the two- and four-chamber views, as previously described. The LA and LV volumes were measured with a match in the same end-diastolic phase defined by mitral valve closure. The intra- and inter-reader reproducibility of the LACI were both good, with ICC of 0.93 (95% confidence interval, CI 0.90–0.96) and 0.81 (95% CI 0.71–0.88), respectively (15). The LACI value is expressed as a percentage, and a higher LACI expresses greater disproportion between the LA and LV volumes at ventricular end diastole, reflecting greater impairment of left atrioventricular coupling.



Outcomes

The MESA outcome ascertainment protocols have been described in detail and are available online.¹ Outcomes of interest were HF, AF, CHD death, and hard CVD (Supplementary material 4). In addition to MESA follow-up examinations every two years, a telephone interviewer contacted each participant every 9–12 months to inquire about interim hospital admissions, cardiovascular outpatient diagnoses, and death. Two physicians reviewed all records for independent endpoint classification and the assignment of event dates. Criteria for hard CVD outcomes included myocardial infarction, resuscitated cardiac arrest, death from coronary disease, and fatal and non-fatal stroke. CHD death included myocardial infarction, chest pain within the 72 hours before death, or a history of CHD and the absence of a non-cardiac cause of death. Criteria for HF as an endpoint included symptomatic HF diagnosed by a physician in a patient receiving medical treatment for HF and exhibiting pulmonary edema/congestion by chest X-ray and/or a dilated LV or poor LV function by echocardiography, or evidence of LV diastolic dysfunction. Criteria for AF as an endpoint required an AF diagnosis according to International Classification of Diseases (ICD)-9 codes.

¹ www.mesa-nhlbi.org

Statistical analysis

The baseline characteristics of the study participants are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) for continuous variables and as counts and percentages for categorical variables in Table 1. The sex hormone levels were positively skewed and thus logarithmically transformed and analyzed per one SD of their natural log. Comparisons employed the χ^2 or Fisher’s exact test for categorical variables and the Student’s *t*-test or Mann–Whitney–Wilcoxon test, as appropriate, for continuous variables. Cox regression models were used to study the associations between the LACI and the outcomes. The proportional hazard assumption was visually tested using Schoenfeld residuals. The cumulative risk of outcomes over the follow-up years, stratified by LACI tertiles, was determined using Kaplan–Meier curves censored at the most recent follow-up. Differences across tertiles were compared using the log-rank test. The associations between LACI or all other LA and LV parameters and time-to-event were analyzed with multivariable Cox survival analyses, adjusting for traditional risk factors at baseline: age, ethnicity, education level, physical activity, menopausal status, hormone therapy (HT) use, diabetes mellitus, current smoking, systolic blood pressure, antihypertensive therapy, body mass index, high-density lipoprotein cholesterol, total cholesterol, lipid-lowering therapy, total testosterone/estradiol ratio, DHEA level, and glomerular filtration rate. Of note, the total testosterone/estradiol ratio was

TABLE 1 Population characteristics of participants at baseline before occurrence of events by incident event categories (n = 2,087).

Parameters	No event (n = 1,772)	HF (n = 83)	AF (n = 176)	CHD death (n = 71)	Hard CVD (n = 155)
Age, years	53.6 ± 10.0	68.1 ± 8.6	69.4 ± 8.1	70.0 ± 8.2	66.0 ± 9.1
Ethnicity (Ca/Ch/AA/Hi), %	39/13/26/22	42/11/28/19	51/9/21/19	38/11/31/20	39/10/26/25
Education					
<High school	374 (21.1)	23 (27.7)	52 (29.5)	21 (29.2)	43 (27.7)
High school, technical school, or associate degree	888 (50.1)	45 (54.2)	93 (52.8)	38 (53.7)	84 (54.2)
College, graduate or professional school	500 (28.2)	15 (18.1)	30 (17.0)	12 (17.1)	28 (18.1)
Hypertension, n (%)	679 (38.3)	58 (69.9)	102 (58.0)	44 (62.4)	93 (60.0)
Systolic blood pressure, mmHg	124 ± 22	133 ± 23	130 ± 21	134 ± 21	131 ± 22
Diastolic blood pressure, mmHg	69 ± 10	71 ± 12	70.0 ± 11	70.0 ± 10	72 ± 11
Body mass index, kg/m ²	28.0 ± 5.6	29.6 ± 5.6	29.1 ± 5.5	28.5 ± 5.4	29.2 ± 6.1
Diabetes mellitus, n (%)	183 (10.3)	21 (25.3)	27 (15.3)	17 (24.2)	35 (22.6)
Smoking status, n (%)	195 (11.0)	10 (12.0)	16 (9.1)	12 (16.3)	22 (14.2)
Heart rate, bpm	64 ± 9	65 ± 11	64 ± 9	64 ± 9	65 ± 10
Total cholesterol, mg/dl	197 ± 34	200 ± 33	192 ± 31	204 ± 39	206 ± 35
HDL cholesterol, mg/dl	58 ± 15	54 ± 13	56 ± 16	53 ± 14	53 ± 14
eGFR*, ml/min/1.73 m ²	80.2 ± 15.8	72.2 ± 19.0	70.4 ± 17.3	72.6 ± 17.2	74.7 ± 18.1
Hypertension medication, n (%)	542 (30.6)	48 (57.8)	90 (51.1)	39 (55.2)	72 (46.5)
Lipid-lowering medication, n (%)	280 (15.8)	16 (19.3)	35 (19.9)	20 (28.2)	33 (21.3)
NT-proBNP, pg/ml	79 (51–109)	192 (102–391)	131 (89–289)	120 (69–229)	104 (66–298)
Agatston score, mean ± SD	46 ± 101	156 ± 316	175 ± 431	122 ± 310	109 ± 212
Framingham CVD risk,%	9.1 ± 8.7	17.2 ± 7.3	16.8 ± 7.8	21.0 ± 7.0	17.1 ± 7.8
CHARGE-AF score	11.5 ± 1.2	12.8 ± 1.0	13.1 ± 1.0	12.9 ± 1.0	12.3 ± 1.1
Baseline LV characteristics					
LV EDVi, ml/m ²	66.2 ± 13.0	71.7 ± 19.0	69.5 ± 17.1	67.5 ± 19.2	66.3 ± 16.0
LVEF,%	63.9 ± 6.1	60.2 ± 8.0	63.5 ± 6.6	61.1 ± 7.8	61.8 ± 7.0
LV mass index, g/m ²	56.1 ± 12.0	70.1 ± 17.2	65.2 ± 15.1	66.3 ± 18.2	65.3 ± 15.3
LVMVR, g/ml	0.88 ± 0.17	1.01 ± 0.22	0.97 ± 0.21	1.00 ± 0.22	0.99 ± 0.20
LVGFI,%	43.9 ± 6.2	36.3 ± 7.0	39.2 ± 6.3	37.0 ± 7.2	37.3 ± 6.4
Baseline LA characteristics					
LA EDVi, ml/m ²	11.2 ± 6.1	16.3 ± 9.8	18.6 ± 11.4	14.2 ± 9.1	13.5 ± 7.6
LA ESVi, ml/m ²	29.8 ± 9.9	35.0 ± 13.6	37.5 ± 15.4	32.3 ± 13.1	31.2 ± 11.6
Peak LA strain,%	39.8 ± 10.6	33.1 ± 11.1	32.0 ± 10.2	33.5 ± 10.8	35.1 ± 11.3
LACI,%	16.7 ± 8.0	22.8 ± 11.8	25.1 ± 13.9	21.0 ± 11.6	20.1 ± 10.3

The comparisons with the no event population that were statistically significant with *p* < 0.05 are shown in bold type. *Estimated glomerular filtration rate (eGFR) was calculated by chronic kidney disease epidemiology collaboration (CKD-EPI) method. AA, African American; AF, atrial fibrillation; Ca, Caucasian; CHD, coronary heart disease; Ch, Chinese American; CVD, cardiovascular disease; HDL, high-density lipoprotein; HF, heart failure; Hi, Hispanic; LA, left atrium; LACI, left atrioventricular coupling index; EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; LV, left ventricle; LVEF, left ventricle ejection fraction; LVGFI, left ventricle global function index; LVMVR, LV mass/LV volume; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

used as a sex hormone covariate in the final model because it was previously described in MESA as the best prognosticator of cardiovascular events in women (6).

Model discrimination was compared using C-statistic. The additional predictive value of the LACI was calculated using C-statistic increment, continuous net reclassification improvement (NRI), and integrative discrimination index (IDI) (25), and compared to the CHARGE-AF score (26), Framingham score (27), Agatston score (28), and LA or

LV parameters. NRI and IDI were computed at 10 years using the R package “survIDINRI” (29). The survival tree method was used to determine the cut-off to transform the LACI into a binary variable with the best predictive value. Stratified analyses were performed in pre-specified subgroups defined by menopausal status and HT use at baseline (because estradiol levels differ substantially among women using versus not using HT) (6, 7). A two-tailed *p*-value < 0.05 was considered statistically significant. All data

were analyzed using R software, version 3.6.1 (R Project for Statistical Computing).

Results

Study population and cardiovascular events

Among the 3,601 women in the MESA cohort, 2,087 (58.0%) underwent a baseline CMR examination and had available outcome data (mean age 61.2 ± 10.1 years). Of these women, 43.5% had hypertension, 11.4% were current smokers, 10.7% had diabetes mellitus, and their mean body mass index was 28.1 ± 5.6 kg/m². At baseline, 35.9% of the women were on antihypertensive therapy, and 16.3% were on lipid-lowering medication. Among the 2,087 women, 415 (19.9%) were pre-menopausal and 1,672 (80.1%) were post-menopausal, including 1,110 (66.4%) using HT and 562 (33.6%) not using HT.

The population characteristics stratified by menopausal status and HT use are presented in **Supplementary material 5**. The baseline characteristics of the population, divided into those who developed AF ($n = 176$, 8.4%), hard CVD ($n = 155$, 7.4%), HF ($n = 83$, 4.0%), and CHD death ($n = 71$, 3.4%) over a mean follow-up period of 13.2 ± 3.3 years, are presented in **Table 1**. The mean follow-up was 11.3 ± 3.8 years for AF and 16.4 ± 1.1 years for other outcomes. When all clinical events were combined, 315 (15.1%) women had a CV event.

Left atrioventricular coupling index distribution and relationship to menopausal status, hormone therapy use, and sex hormone levels

In the entire population, the mean LACI was $17.6 \pm 8.0\%$, and the first to third tertiles of the LACI were ≤ 12.6 , 12.6–19.5, and $>19.5\%$, respectively (**Supplementary material 6**). The mean LACI was $16.7 \pm 8.0\%$ in women with no events. Pre-menopausal women had a lower LACI than post-menopausal women (15.0 ± 7.0 vs. $18.2 \pm 8.7\%$, $p < 0.001$). Among post-menopausal women, women using HT had a lower LACI than women not using HT (17.0 ± 9.0 vs. $18.8 \pm 8.0\%$, $p < 0.001$; **Figure 2**). Regarding sex hormone levels, a higher LACI value was associated with a higher total T level ($p = 0.031$), a higher total testosterone/estradiol ratio ($p = 0.002$), and lower estradiol ($p = 0.022$) and DHEA ($p = 0.042$) levels. The relationship between the LACI and free T, or SHBG levels at baseline were not statistically significant (**Figure 3**).

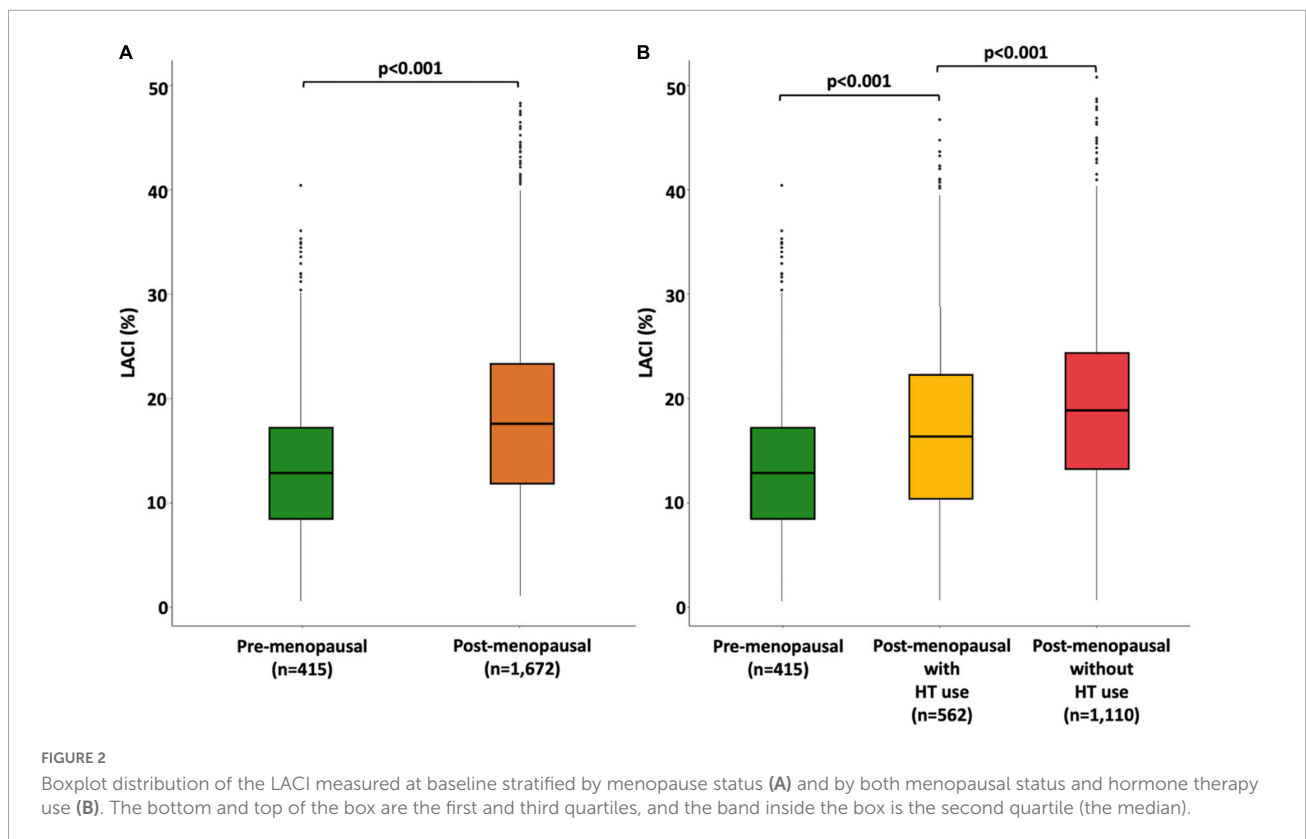
Prognostic value of left atrioventricular coupling index in all women

Unadjusted and adjusted Cox proportional hazard models for the LACI and the main LA and LV parameters are presented in **Table 2** (other LA-LV parameters and biomarkers are presented in **Supplementary material 7**). After adjusting for risk factors, the LACI was positively associated with incident AF (hazard ratio [HR] 1.70; 95% CI 1.51–1.90), incident HF (HR 1.62; 95% CI 1.33–1.97), CHD death (HR 1.36; 95% CI 1.10–1.68), and hard CVD (HR 1.30; 95% CI 1.13–1.51; for all per one SD increment, $p < 0.001$). When the LACI was categorized in tertiles, a LACI value $> 19.5\%$ was associated with incident AF, HF, CHD death, and hard CVD in comparison to the first tertile ($\leq 12.6\%$, all $p < 0.001$; **Figure 4**). Using the survival tree method, the best LACI cut-offs for prediction were as follows: $>28\%$ to predict AF, $>26\%$ for HF, $>25\%$ for CHD death, and $>26\%$ for hard CVD. Using the composite outcome cut-off, including HF, AF, CHD death, and hard CVD, an increased LACI of $>25\%$ was independently associated with an increased occurrence of AF (HR 2.93; 95% CI 2.11–4.08, $p < 0.001$), HF (HR 2.45; 95% CI 1.54–3.91, $p < 0.001$), CHD death (HR 1.98; 95% CI 1.11–3.52, $p = 0.023$), and hard CVD (HR 1.59; 95% CI 1.11–2.29, $p = 0.012$; **Table 2** and **Supplementary material 8**).

Prognostic value of left atrioventricular coupling index according to menopausal status and hormone therapy use

When the best LACI cut-off was used, it was found that post-menopausal women with a LACI $> 25\%$ presented a higher risk of AF, HF, CHD death, and hard CVD than pre-menopausal women or post-menopausal women with a LACI $\leq 25\%$ ($p < 0.001$, **Supplementary material 9**). As already mentioned, to account for the fact that estradiol levels differ considerably between women using HT and those not using HT, we performed stratified analyses to compare pre-menopausal women and post-menopausal women using HT to post-menopausal women not using HT. The global prognostic value of the LACI was homogeneous in these two groups (**Table 3**).

In women with a LACI $> 25\%$, the cumulative hazard was higher for post-menopausal women not using HT than for pre-menopausal women or post-menopausal women using HT ($p < 0.001$). Regardless of whether the women were pre-menopausal, menopausal and not using HT, or post-menopausal and not using HT, the cumulative hazard was higher for women with a LACI $> 25\%$ than for women with a LACI $\leq 25\%$ ($p < 0.001$; **Figure 5**).



Improvement in risk prediction with the addition of left atrioventricular coupling index

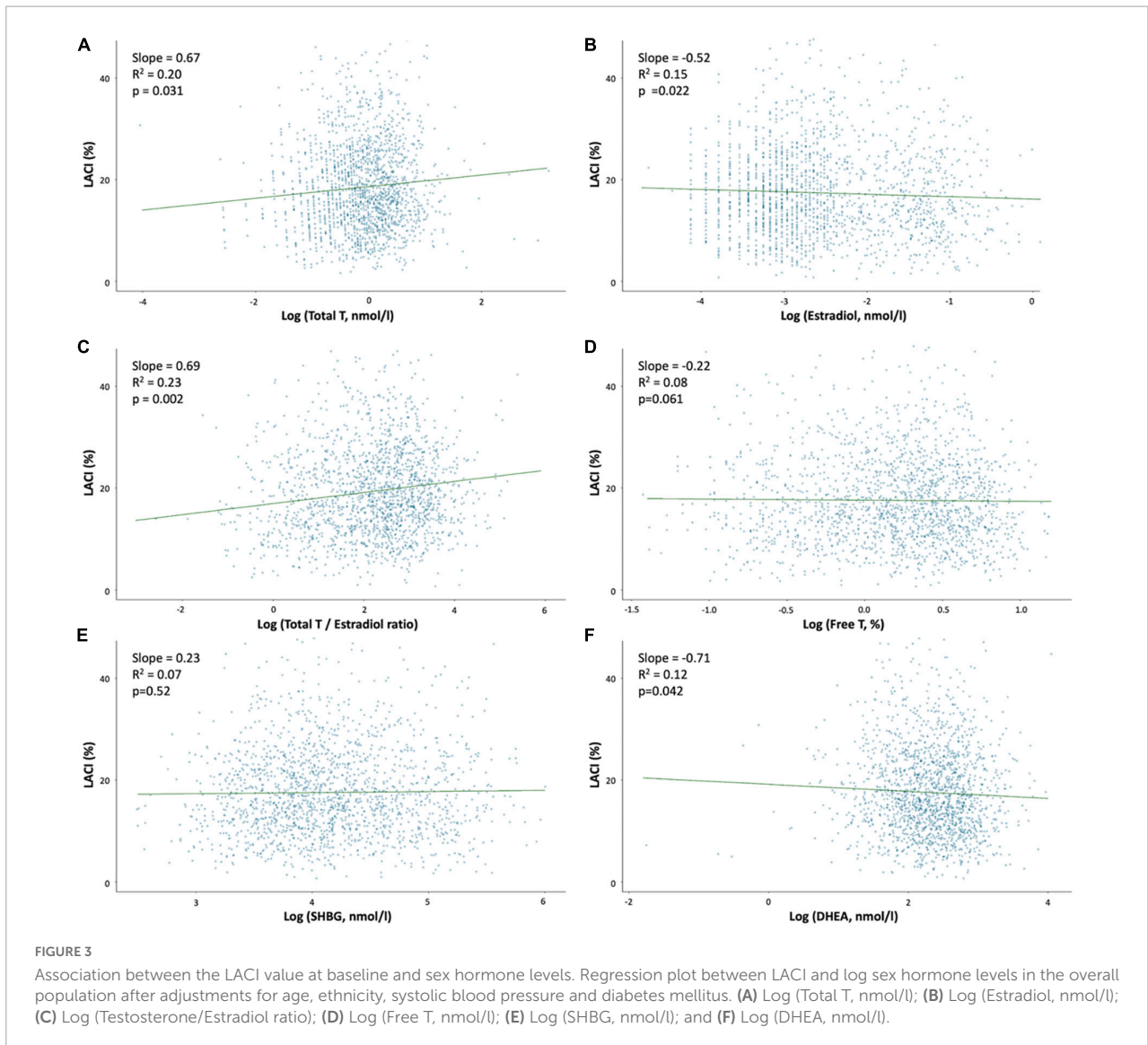
The multivariable model with the LACI showed significant improvement in model discrimination and reclassification compared to the model with traditional risk factors for predicting AF (C-statistic: 0.82 vs. 0.79; NRI = 0.325; IDI = 0.036), HF (C-statistic: 0.84 vs. 0.81; NRI = 0.571; IDI = 0.023), CHD death (C-statistic: 0.87 vs. 0.85; NRI = 0.506; IDI = 0.012), and hard CVD (C-statistic: 0.78 vs. 0.76; NRI = 0.229; IDI = 0.012). The LACI also had better discrimination and reclassification for these outcomes than the model with each LA or LV parameter and the other biomarkers and scores (Table 2 and Supplementary material 10).

Discussion

This study focused on a large multi-ethnic population of pre- and post-menopausal women aged 45–84 years who were free of clinical CVD at baseline. The participants were followed for more than 13 years. The main findings were as follows: (i) the LACI showed the greatest association with incident AF, HF, CHD death, and hard CVD, improving model discrimination and reclassification of cardiovascular event risk

above menopausal status, traditional cardiovascular risk factors, and sex hormone levels; (ii) the prognostic value of the LACI was homogeneous in both pre-menopausal and post-menopausal women; (iii) post-menopausal women had worse left atrioventricular function, defined by a higher LACI value, than pre-menopausal women; (iv) post-menopausal women using HT had better left atrioventricular function, defined by a lower LACI value, than post-menopausal women not using HT; and (v) the LACI was positively associated with total testosterone and DHEA levels, but inversely associated with estradiol level. To our knowledge, the prognostic value of a left atrioventricular coupling index in pre- and post-menopausal women and the association of LACI and sex hormone levels have not been previously well-established.

In CVD pathophysiology, specific biological mechanisms have been described in women due to the role of endogenous sex hormones (1, 5, 6, 8, 30). However, our analysis of pre- and post-menopausal women has shown that the LACI has a higher prognostic value and improves model discrimination and reclassification in predicting the risk of outcomes compared to individual LA or LV parameters. These features are maintained even after adjusting for traditional risk factors, menopausal status, HT use, and sex hormone levels (total testosterone/estradiol ratio). Therefore, this study highlights the prognostic importance of atrioventricular coupling, reflected by the intricate hemodynamic interactions between the left



atrium and ventricle during LV diastole (31), in stratifying cardiovascular event risk in peri- and post-menopausal women.

We also investigated the best LACI cut-off threshold, and found that a LACI > 25% was the best cut-off for the composite of all four cardiovascular outcomes. This is in line with the prior study that defined the LACI in all the MESA population, including both men and women (15). Moreover, the normal value of LACI already published is 16 ± 8% (15). Interestingly, regardless of whether women were menopausal and not using HT, or pre-menopausal or post-menopausal not using HT, the risk of outcomes was higher for women with a LACI > 25% than for women with a LACI ≤ 25%. In contrast, among all women with a LACI > 25%, post-menopausal women not using HT had a higher outcomes rate than pre-menopausal women or post-menopausal women using HT. All these findings support the notion that the LACI has an additional prognostic

value above that of menopausal status and HT use; however, menopausal status and HT use also have important prognostic value beyond the LACI.

In this study, when the LACI value was used as a marker of left atrioventricular function (19), it was found that post-menopausal women had worse left atrioventricular function than pre-menopausal women (18.2 vs. 15.0%). Given that menopause is also a marker of aging, these findings are consistent with those of a prior study that used CMR imaging of 40 healthy individuals, including 17 women, to investigate the effects of aging on left atrioventricular coupling (14). The oldest participants had larger LA volumes, smaller LV volumes, and larger LA/LV end-diastolic volume ratios (27 ± 6 vs. 19 ± 3%; *p* < 0.001).

Beyond menopausal status, we also assessed left atrioventricular function according to HT use, because estradiol

TABLE 2 Univariable and multivariable analysis of CV events occurrence according to left atrioventricular coupling index and other LA or LV parameters in all women (n = 2,087).

CMR parameters	Unadjusted			Adjusted*		
	HR (95%CI)	p-value	C-index (95%CI)	HR (95%CI)	p-value	C-index (95%CI)
Incident AF						
-LACI [†] ,% (per 1 SD)	1.99 (1.73–2.13)	<0.001	0.68 (0.64–0.72)	1.70 (1.51–1.90)	<0.001	0.82 (0.80–0.85)
-LACI cut-off > 25% [‡]	4.18 (3.05–5.73)	<0.001	0.62 (0.59–0.66)	2.93 (2.11–4.08)	<0.001	0.80 (0.77–0.82)
-LA EDVi, ml/m ² (per 1 SD)	1.61 (1.46–1.79)	<0.001	0.64 (0.60–0.68)	1.45 (1.31–1.61)	<0.001	0.81 (0.78–0.83)
-LV EDVi, ml/m ² (per 1 SD)	0.86 (0.76–0.98)	0.031	0.57 (0.53–0.61)	0.97 (0.84–1.12)	0.67	0.79 (0.76–0.81)
-LVEF,% (per 1 SD)	0.98 (0.86–1.13)	0.82	0.50 (0.45–0.54)	0.98 (0.86–1.11)	0.73	0.79 (0.77–0.82)
-LV mass, g/m ² (per 1 SD)	1.03 (0.90–1.19)	0.63	0.50 (0.46–0.54)	0.99 (0.87–1.14)	0.92	0.79 (0.76–0.81)
-Peak LA strain,% (per 1 SD)	0.58 (0.49–0.64)	<0.001	0.64 (0.60–0.68)	0.71 (0.60–0.83)	<0.001	0.80 (0.77–0.82)
Incident HF						
-LACI [†] ,% (per 1 SD)	2.05 (1.68–2.37)	<0.001	0.71 (0.65–0.76)	1.62 (1.33–1.97)	<0.001	0.84 (0.80–0.88)
-LACI cut-off > 25% [‡]	3.94 (2.54–6.10)	<0.001	0.63 (0.58–0.69)	2.45 (1.54–3.91)	<0.001	0.83 (0.79–0.87)
-LA EDVi, ml/m ² (per 1 SD)	1.77 (1.54–2.04)	<0.001	0.69 (0.63–0.75)	1.56 (1.32–1.83)	<0.001	0.83 (0.79–0.87)
-LV EDVi, ml/m ² (per 1 SD)	1.11 (0.89–1.38)	0.37	0.50 (0.43–0.58)	1.24 (0.99–1.56)	0.07	0.81 (0.77–0.85)
-LVEF,% (per 1 SD)	0.70 (0.59–0.81)	<0.001	0.59 (0.52–0.67)	0.69 (0.59–0.81)	<0.001	0.83 (0.79–0.87)
-LV mass, g/m ² (per 1 SD)	1.68 (1.40–2.00)	<0.001	0.63 (0.56–0.69)	1.44 (1.18–1.75)	<0.001	0.83 (0.79–0.87)
-Peak LA strain,% (per 1 SD)	0.61 (0.46–0.80)	<0.001	0.63 (0.57–0.69)	0.74 (0.58–0.96)	0.021	0.82 (0.80–0.85)
CHD death						
-LACI [†] ,% (per 1 SD)	1.80 (1.49–2.18)	<0.001	0.67 (0.61–0.74)	1.36 (1.10–1.68)	<0.001	0.87 (0.84–0.90)
-LACI cut-off > 25% [‡]	2.66 (1.62–4.38)	<0.001	0.59 (0.54–0.65)	1.98 (1.11–3.52)	0.023	0.86 (0.83–0.90)
-LA EDVi, ml/m ² (per 1 SD)	1.48 (1.24–1.76)	<0.001	0.62 (0.55–0.69)	1.28 (1.05–1.56)	0.009	0.87 (0.84–0.89)
-LV EDVi, ml/m ² (per 1 SD)	0.86 (0.69–1.07)	0.25	0.50 (0.43–0.58)	1.05 (0.82–1.33)	0.71	0.85 (0.82–0.88)
-LVEF,% (per 1 SD)	0.93 (0.74–1.17)	0.54	0.50 (0.42–0.57)	0.84 (0.67–1.05)	0.13	0.85 (0.82–0.89)
-LV mass, g/m ² (per 1 SD)	1.25 (1.00–1.55)	0.049	0.52 (0.44–0.60)	1.11 (0.89–1.40)	0.35	0.85 (0.82–0.89)
-Peak LA strain,% (per 1 SD)	0.83 (0.64–1.08)	0.17	0.57 (0.50–0.64)	0.99 (0.79–1.24)	0.93	0.85 (0.82–0.88)
Hard CVD						
-LACI [†] ,% (per 1 SD)	1.65 (1.45–1.88)	<0.001	0.64 (0.60–0.69)	1.30 (1.13–1.51)	<0.001	0.78 (0.74–0.81)
-LACI cut-off > 25% [‡]	2.37 (1.68–3.34)	<0.001	0.58 (0.54–0.61)	1.59 (1.11–2.29)	0.012	0.76 (0.73–0.80)
-LA EDVi, ml/m ² (per 1 SD)	1.33 (1.16–1.52)	<0.001	0.60 (0.55–0.64)	1.19 (1.04–1.36)	0.014	0.77 (0.74–0.80)
-LV EDVi, ml/m ² (per 1 SD)	0.93 (0.81–1.06)	0.45	0.55 (0.51–0.60)	0.88 (0.74–1.05)	0.15	0.76 (0.72–0.79)
-LVEF,% (per 1 SD)	0.86 (0.74–1.00)	0.045	0.55 (0.51–0.60)	0.83 (0.72–0.96)	0.011	0.76 (0.72–0.80)
-LV mass, g/m ² (per 1 SD)	1.15 (0.98–1.34)	0.08	0.51 (0.46–0.56)	1.05 (0.89–1.23)	0.33	0.76 (0.72–0.79)
-Peak LA strain,% (per 1 SD)	0.88 (0.74–1.05)	0.15	0.55 (0.51–0.60)	1.00 (0.86–1.17)	0.98	0.76 (0.72–0.79)

*Adjusted model included age, ethnicity, education level, physical activity, menopausal status, hormone therapy (HT) use, diabetes mellitus, current smoking, systolic blood pressure, anti-hypertensive therapy, body mass index, high-density lipoprotein cholesterol, total cholesterol, lipid-lowering therapy, total testosterone/estradiol ratio, DHEA level, and glomerular filtration rate.

[†]LACI used as continuous variable.

[‡]LACI used as binary variable defined by a cut-off > 25%. -All LV parameters, LA parameters and LACI values were normalized according to the following formula: (parameter–mean value)/standard. AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; LA, left atrium; LACI, left atrioventricular coupling index; EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; LV, left ventricle; LVEF, left ventricle ejection fraction.

Bold represent the statistically significant results.

levels differ substantially among women who use HT and those who do not. This analysis showed that among post-menopausal women, those using HT had better left atrioventricular function, defined by a lower LACI value, than women not using HT. However, the significant difference in LACI values between pre-menopausal women and post-menopausal women using HT suggests that HT may not exert the same physiological effects as endogenous sex hormones. Consistently, some studies

have reported the effects on CVD risk of formulations of estrogen and progestin and the time since HT initiation (32). Beyond the previously described effects of sex hormones on LV structure (7), these findings suggest a potential additional effect of sex hormones on left atrioventricular coupling in peri- and post-menopausal women.

Regarding the association between sex hormone levels and heart structure, recent studies have shown that higher

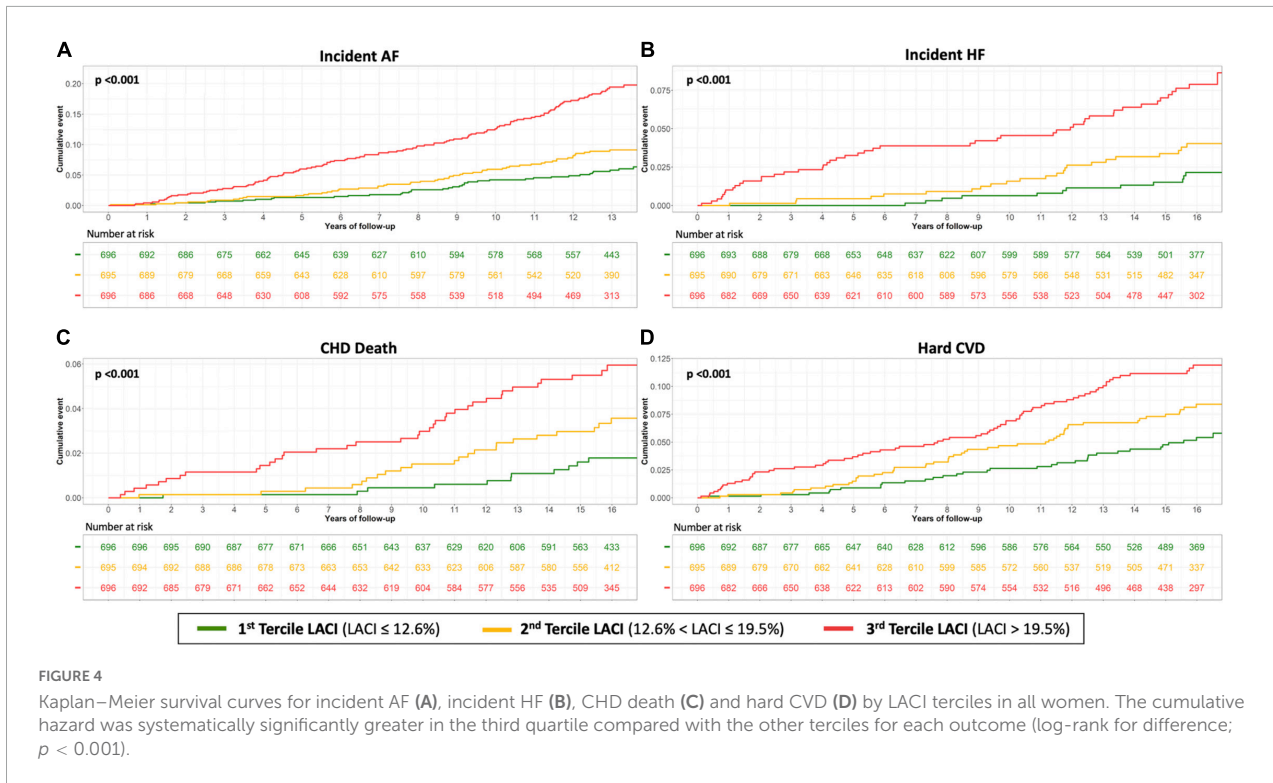
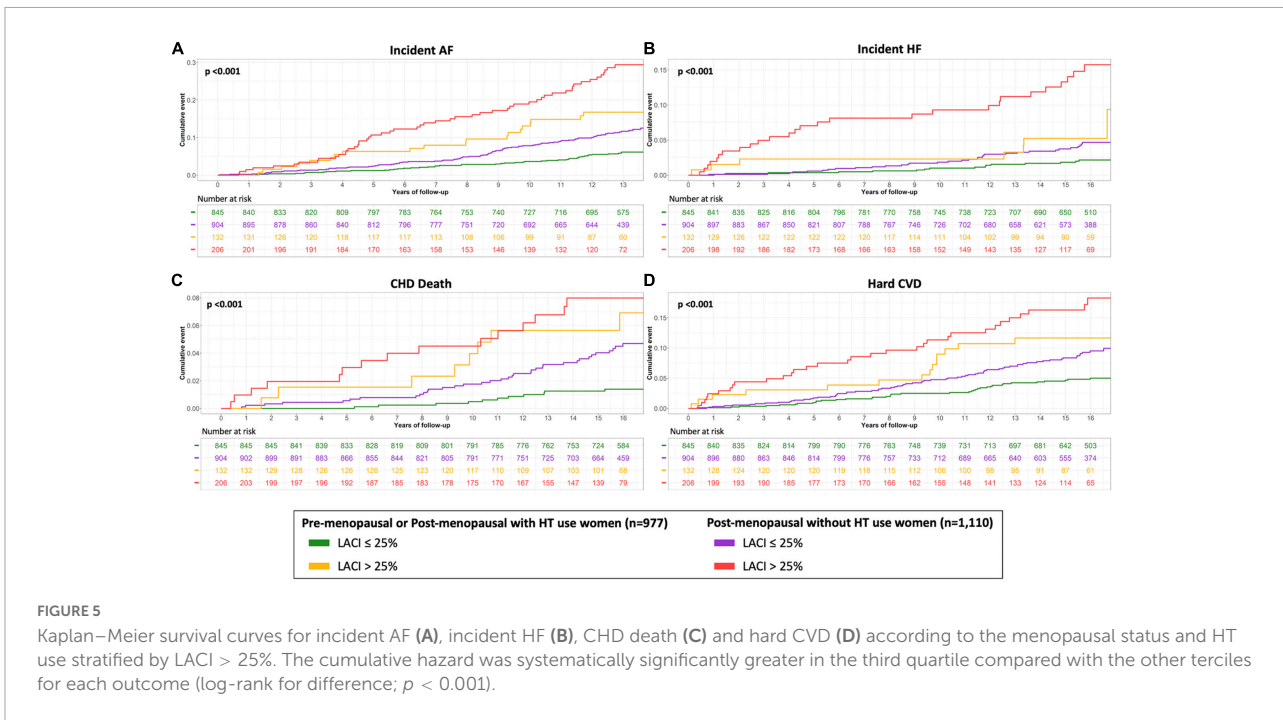


TABLE 3 Univariable and multivariable analysis of left atrioventricular coupling index for prediction of CV events stratified by menopausal status ($n = 2,087$).

Outcomes	Unadjusted			Adjusted		
	HR (95%CI)	p-value	C-index (95%CI)	HR (95%CI)	p-value	C-index (95%CI)
Incident AF						
-LACI* in pre-menopausal women or post-menopausal women with HT use ($n = 977$)	1.98 (1.42–2.52)	<0.001	0.68 (0.62–0.74)	1.68 (1.18–1.58)	0.003	0.82 (0.80–0.85)
-LACI* in post-menopausal women without HT use ($n = 1,110$)	2.02 (1.56–2.36)	<0.001	0.69 (0.64–0.73)	1.73 (1.34–1.73)	<0.001	0.83 (0.81–0.85)
Incident HF						
-LACI* in pre-menopausal women or post-menopausal women with HT use ($n = 977$)	1.82 (1.12–2.07)	0.004	0.70 (0.62–0.77)	1.38 (1.03–1.79)	0.022	0.83 (0.77–0.88)
-LACI* in post-menopausal women without HT use ($n = 1,110$)	2.22 (1.63–2.33)	<0.001	0.72 (0.64–0.78)	1.77 (1.23–2.28)	<0.001	0.85 (0.78–0.89)
CHD death						
-LACI* in pre-menopausal women or post-menopausal women with HT use ($n = 977$)	1.82 (1.21–2.50)	<0.001	0.67 (0.59–0.76)	1.32 (1.02–1.76)	0.034	0.86 (0.80–0.92)
-LACI* in post-menopausal women without HT use ($n = 1,110$)	1.77 (1.26–2.35)	<0.001	0.67 (0.60–0.76)	1.30 (1.04–1.70)	0.013	0.86 (0.81–0.91)
Hard CVD						
-LACI* in pre-menopausal women or post-menopausal women with HT use ($n = 977$)	1.50 (1.15–1.88)	0.003	0.63 (0.58–0.69)	1.28 (1.03–1.81)	0.044	0.76 (0.71–0.80)
-LACI* in post-menopausal women without HT use ($n = 1,110$)	1.72 (1.42–2.39)	<0.001	0.65 (0.60–0.70)	1.38 (1.09–1.98)	0.025	0.78 (0.72–0.81)

*LACI used as continuous variable, % (per 1 SD). -LACI values were normalized according to the following formula: (parameter–mean value)/standard deviation. Adjusted model included age, ethnicity, education level, physical activity, diabetes mellitus, current smoking, systolic blood pressure, anti-hypertensive therapy, body mass index, high-density lipoprotein cholesterol, total cholesterol, lipid-lowering therapy, total testosterone/estradiol ratio, DHEA level, and glomerular filtration rate. AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; LACI, left atrioventricular coupling index. Bold represent the statistically significant results.



free testosterone and lower SHBG levels are associated with greater LV mass and an increased LV mass-volume-ratio (concentric remodeling) (7), higher endothelial dysfunction assessed using brachial artery flow-mediated dilation (33), higher LV diastolic dysfunction (34), and greater coronary artery calcium score progression (35). However, total testosterone and estradiol levels have not been associated with LV structure (7). Despite the contradictory outcomes of prospective studies that have assessed the plausible pathological pathways that link endogenous sex hormones and clinical CVD events, the MESA has recently shown that in post-menopausal women, a higher total testosterone level and a lower estradiol level are associated with an increased risk of CVD (6). However, the study also found that free testosterone and SHBG levels are not prognosticators of CVD (6). Together, these results suggest that total testosterone and estradiol levels influence CVD risk via mechanisms other than modification of LV structure.

In the current study, a higher LACI value was significantly associated with a higher DHEA level, a higher total testosterone level, a lower estradiol level, and thus a higher total testosterone/estradiol ratio. Based on these results, we hypothesize that these sex hormones influence the left atrioventricular coupling function. Indeed, estradiol can downregulate angiotensin receptors, improve vascular endothelium function, protect against vascular injury, and inhibit adverse LV remodeling processes (8). In contrast, testosterone can increase platelet aggregation via upregulation of thromboxane and induce vasoconstriction (36). The effect of DHEA on CVD has not yet been defined. It was hypothesized that lower DHEA levels may be associated with

an increased risk of cardiovascular events (37); however, this association has been disproved by numerous studies, particularly those conducted with elderly women (38). Therefore, in addition to these reported mechanisms by which estradiol and testosterone may play a prognostic role for peri- and post-menopausal women, the current findings suggest that the abrupt loss of estradiol at menopause and the potential increase in total testosterone may be significant contributors to left atrioventricular coupling. Moreover, the LACI was not associated with free testosterone and SHBG levels in this study, which supports the hypothesis that total testosterone and estradiol influence CVD risk through effects on left atrioventricular coupling and not just the modification of LV structure.

Because the LACI is an independent prognosticator of cardiovascular events, even after adjusting for the total testosterone/estradiol ratio, the association between the LACI and both the total testosterone and estradiol levels supports the hypothesis that these hormones impact left atrioventricular coupling. Therefore, all these findings emphasize the complexity of the female hormonal system during the peri- and post-menopausal states; there are hormones acting independently and in combination. The findings suggest that the abrupt modification of sex hormone levels during menopause could critically influence left atrioventricular coupling, thus explaining the increase in cardiovascular events in older women. Beyond menopausal status and sex hormone levels, the LACI may help identify women who have an increased CVD risk and who may benefit from additional risk-reducing strategies.

Study limitations

This study has several limitations. First, the general applicability of these findings may be limited by survivor biases. The women who participated had no known CVD at baseline; therefore, the older women undergoing CMR in this cohort represent a healthier sample than the general older population. Second, the LACI was investigated as a primary prevention tool in the early detection of CVD risk in asymptomatic women without CVD. Therefore, the LACI would not be the ideal parameter for assessing a woman with CVD and/or both LA and LV enlargements. Third, menopausal status was self-reported, which introduces a risk of reporting bias. To minimize this bias we corrected self-reported menopausal status using an algorithm based on age, self-reported hysterectomy, bilateral oophorectomy, and menopausal age (6). Moreover, a single measurement of sex hormones was performed at baseline, by radioimmunoassay and not mass spectrometry, which is the current gold standard. Fourth, two-dimensional instead of three-dimensional methods were used to measure LA volumes, which may have underestimated volumes by 11.5–20% (39). Nevertheless, this method has been validated (22, 23). In addition, echocardiographical data were not collected in MESA study. Fifth, this study was designed to assess the prognostic impact of different parameters on the occurrence of incident AF, but the management of AF by ablation or medical treatment of these patients was not collected. Sixth, the optimal cut-off value for LACI was not validated using an external validation cohort. However, to our knowledge, there is no existing cohort of peri-menopausal women without known CVD with CMR at baseline and with such an important median long-term follow-up. Further studies will therefore need to validate these results. Since CMR is not widely accessible, the use of the LACI as a screening tool in the general population should be investigated using echocardiography.

Conclusion

In a large multi-ethnic study population of pre-menopausal and post-menopausal women who were free of clinical CVD at baseline, a higher LACI (measured using CMR imaging) was associated with a higher risk of incident AF, HF, CHD death, and hard CVD during a 13-year average follow-up and this association did not vary by menopause status. Beyond menopausal status and HT use, the addition of the LACI to risk prediction models for these outcomes showed improvements in model discrimination and reclassification of cardiovascular event risks. Finally, the association between the LACI and total testosterone and estradiol levels suggests a potential effect of these hormones on left atrioventricular coupling, which should be confirmed in further studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by IRB of MESA study. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TP and JL conceived the study design. TP, EM, BV, and JL analyzed data and drafted the manuscript with critical revision. As authors, we attest to each of our substantial contributions to the manuscript and revision. All authors participated in the discussion of the concept of the study and read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2022.1066849/full#supplementary-material>

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Partie 5 :

Étude n°4 : Valeur pronostique du changement annuel du LACI pour prédire le risque de fibrillation atriale

Change in Left Atrioventricular Coupling Index to Predict Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis (MESA).

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Radiology. 2022;303(2):317-326. doi: 10.1148/radiol.210315.

Cette quatrième étude se propose d’aller au-delà de l’intérêt de la mesure de notre indice de couplage auriculo-ventriculaire gauche, le LACI, à un instant donné, mais d’investiguer la valeur pronostique de son évolution à l’aide de données longitudinales répétées dans le temps.

Ainsi, l’objectif de cette étude est d’étudier la valeur pronostique d’un indice de couplage auriculo-ventriculaire gauche (LACI) et la variation annualisée moyenne du LACI (Δ LACI) mesurés par IRM cardiaque pour prédire l’incidence de la fibrillation atriale dans un échantillon de population de l’étude MESA. Dans une analyse secondaire de la MESA prospective, 1911 participants à l’étude sans fibrillation atriale ni maladie cardiovasculaire cliniquement reconnue au départ ont eu un LACI évalué par IRM cardiaque au départ (examen 1, 2000-2002) puis 10 ans plus tard (examen 5, 2010 –2012). Le LACI a été défini comme le rapport des volumes télédiastoliques LA sur VG. Des modèles de risque

proportionnel de Cox univariés et multivariés ont été utilisés pour évaluer les associations de LACI et de Δ LACI moyen avec la fibrillation atriale.

Parmi les 1911 participants, 87 événements incidents de fibrillation atriale se sont produits après la deuxième imagerie. Après ajustement pour les facteurs de risque traditionnels, une valeur plus élevée du LACI et du Δ LACI étaient indépendamment associés à la fibrillation atriale (HR, 1,69 ; IC à 95 % [1,46, 1,96] et 1,71 ; IC à 95 % [1,50, 1,94], respectivement ; les deux $p < 0.001$). Les modèles ajustés pour LACI et Δ LACI ont montré une amélioration de la discrimination du modèle par rapport au modèle de score de risque de fibrillation atriale (*Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation*, ou *CHARGE-AF*, score) actuellement utilisé (aire sous la courbe caractéristique de fonctionnement du récepteur [ASC], 0,78 contre 0,74 ; et ASC, 0,80 contre 0,74, respectivement ; les deux $p < 0,001$); et au modèle final comprenant des paramètres de l'oreillette et du ventricule gauches individuels pour prédire l'incidence de la fibrillation atriale (AUC, 0,78 contre 0,76 ; et AUC, 0,80 contre 0,78, respectivement ; les deux $p < 0,001$). Au total, le couplage auriculo-ventriculaire (LACI) et le changement annuel du LACI étaient de puissants prédicteurs de la fibrillation auriculaire. Les deux avaient une valeur pronostique additionnelle pour prédire la FA par rapport aux facteurs de risque traditionnels, et une discrimination supérieure par rapport au score *Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation*, ou *CHARGE-AF*, et aux paramètres de l'oreillette gauche ou du ventricule gauche évalué individuellement.

En résumé, dans cette quatrième étude, nous avons démontré la valeur pronostique indépendante à la fois d'un indice de couplage auriculo-ventriculaire gauche (LACI) et de la variation annualisée moyenne de ce couplage (Δ LACI) pour prédire la fibrillation auriculaire

dans une population multiethnique sans maladie cardiovasculaire clinique au moment de l'inclusion.

Change in Left Atrioventricular Coupling Index to Predict Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Conflicts of interest are listed at the end of this article.

See also the editorial by Leiner in this issue.

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Background: Left atrial (LA) and left ventricular (LV) structural and functional parameters have independent prognostic values as predictors of atrial fibrillation (AF).

Purpose: To investigate the prognostic value of a left atrioventricular coupling index (LACI) and average annualized change in LACI (hereafter, Δ LACI) measured by cardiac MRI to predict incident AF in a population-based sample from the Multi-Ethnic Study of Atherosclerosis (MESA).

Materials and Methods: In a secondary analysis of the prospective MESA, 1911 study participants without clinically recognized AF and cardiovascular disease at baseline had LACI assessed with cardiac MRI at baseline (examination 1, 2000–2002) and 10 years later (examination 5, 2010–2012). LACI was defined as the ratio of LA to LV end-diastolic volumes. Univariable and multivariable Cox proportional hazard models were used to evaluate the associations of LACI and average Δ LACI with incident AF.

Results: Among the 1911 participants (mean age, 59 years \pm 9 [standard deviation]; 907 men), 87 incident AF events occurred over 3.9 years \pm 0.9 after the second imaging (examination 5). After adjustment for traditional risk factors, greater LACI and Δ LACI were independently associated with AF (hazard ratio, 1.69 [95% CI: 1.46, 1.96] and 1.71 [95% CI: 1.50, 1.94], respectively; both $P < .001$). Adjusted models for LACI and Δ LACI showed improvement in model discrimination compared with currently used AF risk score (Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation, or CHARGE-AF, score) model (area under receiver operating characteristic curve [AUC], 0.78 vs 0.74; and AUC, 0.80 vs 0.74, respectively; both $P < .001$); and to the final model including individual LA or LV parameters for predicting AF incidence (AUC, 0.78 vs 0.76; and AUC, 0.80 vs 0.78, respectively; both $P < .001$).

Conclusion: Atrioventricular coupling (left atrioventricular coupling index [LACI]) and coupling change (annual change in LACI) were strong predictors for atrial fibrillation (AF) in a multiethnic population. Both had incremental prognostic value for predicting AF over traditional risk factors, and superior discrimination compared with the Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation, or CHARGE-AF, score and to individual left atrial or left ventricular parameters.

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Online supplemental material is available for this article.

Atrial fibrillation (AF) is the most common cardiac arrhythmia; 6–12 million people will be diagnosed with this condition in the United States by 2050 and 17.9 million in Europe by 2060 (1). AF is therefore a public health problem with important economic burden caused by morbidity and mortality associated with increased risks of stroke and heart failure (1–4).

To address the need for early detection of participants at risk for AF, several studies have assessed left atrial (LA) structure and function by cardiac MRI (5–7). Indeed, LA volumes, peak LA strain, and LA ejection fractions have shown prognostic value in predicting the occurrence of AF independent of traditional risk factors (5,6). These findings suggest that adverse LA remodeling facilitates initiation of

AF by promoting ectopic triggers and altering the wavelength of re-entrant circuits (7). However, many studies emphasize that AF does not occur exclusively because of adverse LA remodeling (8–11). Indeed, left ventricular (LV) diastolic dysfunction has been established as a prognosticator of AF (8–11). Therefore, LV diastolic dysfunction may impair left heart performance by uncoupling functional performances of the two chambers leading to AF. Atrioventricular coupling is complex because LA and LV chamber filling, emptying, and active contraction are not synchronous.

Although LA and LV parameters have independent prognostic values for predicting AF, the inherently connected physiologic relationship between the LA and the

Abbreviations

AF = atrial fibrillation, CHARGE-AF = Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation, HR = hazard ratio, LA = left atrium, LACI = left atrioventricular coupling index, LACI₁₀ = LACI value measured after 10 years, LV = left ventricle, MESA = Multi-Ethnic Study of Atherosclerosis

Summary

In individuals without cardiovascular disease, the left atrioventricular coupling index and its annual change have incremental prognostic value to predict incident atrial fibrillation over traditional risk factors.

Key Results

- In a secondary analysis of the prospective Multi-Ethnic Study of Atherosclerosis (MESA), a left atrioventricular coupling index (LACI) was tested at cardiac MRI in 1911 individuals without cardiovascular disease at enrollment.
- LACI and its annual change were independently associated with the occurrence of atrial fibrillation (AF) (hazard ratio, 1.69 and 1.71, respectively; both *P* < .001).
- LACI showed an incremental long-term prognostic value over and above traditional clinical risk factors of AF (area under receiver operating characteristic curve, 0.78 vs 0.74, respectively; *P* < .001).

LV (12,13) suggests that the assessment of left atrioventricular coupling alterations could better reflect left heart dysfunction and be a better predictor of incident AF.

Previous studies have also shown the superiority of longitudinal evaluations of change in LA parameters to predict AF (6,14–16). Therefore, longitudinal assessment of atrioventricular coupling could be more effective in risk stratification of incident AF among healthy individuals. On the basis of this rationale, we designed an analysis to examine the associations of the left atrioventricular coupling index (LACI) and change in LACI with incident AF in a prospective population study of individuals without history of heart disease at baseline. Specifically, we aimed to investigate the prognostic value of LACI and the average annualized change in LACI (hereafter, ΔLACI) measured at cardiac MRI, for predicting incident AF in the Multi-Ethnic Study of Atherosclerosis (MESA).

Materials and Methods

Study Sample

The MESA (*ClinicalTrials.gov* identifier: NCT00005487) is a prospective, population-based multiethnic (White, African American, Chinese American, and Hispanic) cohort study of subclinical cardiovascular disease, and the study design was previously described in detail

(<https://www.mesa-nhlbi.org>) (17). In summary, between 2000 and 2002 (examination 1), 6814 men and women from age 45 to 84 years and free of clinical cardiovascular disease at enrollment were recruited from six U.S. field centers (Baltimore, Md; Chicago, Ill; Forsyth County, NC; Los Angeles County, Calif; Northern Manhattan, NY; and St Paul, Minn). Examination 1 was followed by examinations 2 (years 2002–2004), 3 (years 2004–2005), 4 (years 2005–2007), and 5 (years 2010–2012). The methods of baseline characteristics and outcome collection are detailed in Appendix E1 (online). In this secondary analysis of the prospective MESA, we included all consecutive participants with at least two cardiovascular MRI examinations (examinations 1 and 5 after 10 years). Participants provided written informed consent. Study protocols were approved by the institutional review boards of each participating field center, with Health Insurance Portability and Accountability Act guidelines compliance.

Participants were excluded if they did not undergo the second cardiac MRI examination, their images were missing or not of sufficient quality to allow measurement of LA and LV volumes, or they developed incident AF between examinations 1 and 5 (Fig 1).

Cardiac MRI Protocol

The MESA cardiac MRI protocol has been described in detail previously (18). Briefly, cardiac MRI was performed at six MESA field centers by using 1.5-T scanners (Appendix E2 [online]). Long-axis cine images were obtained at two- and four-chamber views by using electrocardiography-gated fast gradient-echo pulse sequences. A stack of short-axis cine images were acquired to encompass both ventricles, and LV end-diastolic volume was measured by using cardiac image modeler software (CIM version 6.0; University of Auckland, New Zealand). The cine images

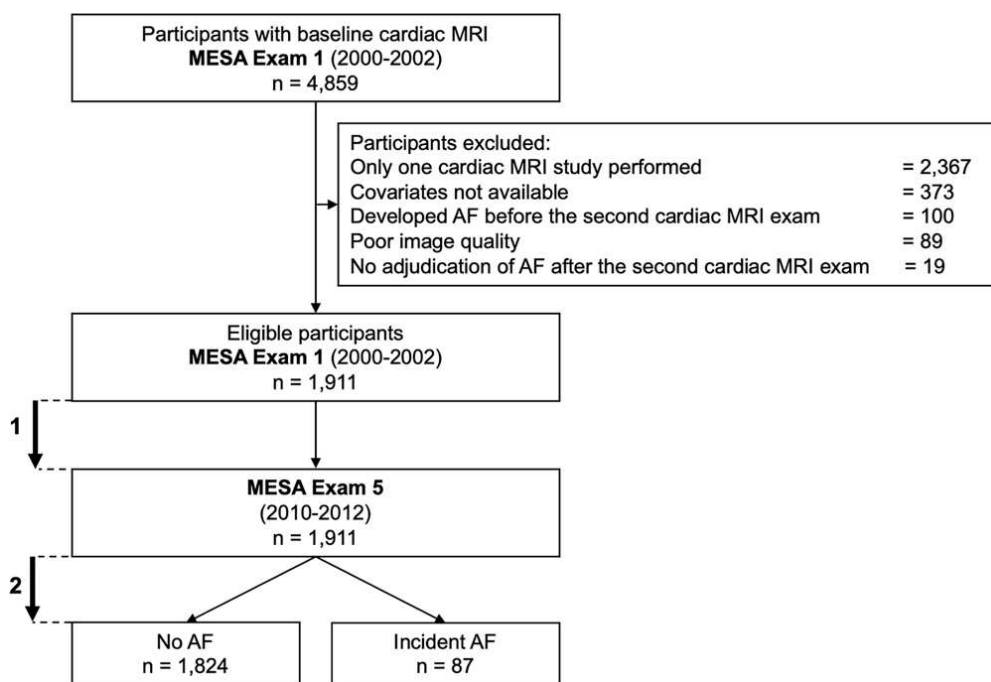


Figure 1: Flowchart of the study. Mean time between baseline and second cardiac MRI examinations, 9.6 years ± 0.4 (1). Mean time of AF follow-up: 3.9 years ± 0.9 after the second cardiac MRI examination (2). AF = atrial fibrillation, MESA = Multi-Ethnic Study of Atherosclerosis.

were acquired with a temporal resolution of approximately 50 msec. Cardiac MRI examinations were performed only in patients in sinus rhythm. MRI sequence parameters are detailed in Table E1 (online).

Image Analysis

Images were read at the central MESA cardiac MRI review center at Johns Hopkins University (Baltimore, Md) (Appendix E2 [online]). Multimodality tissue tracking software (MTT version 6.0; Toshiba Medical Systems) was used to quantify LA volume and strain at two- and four-chamber cine cardiac MRI (Appendix E3 [online]). This method has been validated previously with good to excellent intra- and interreader reproducibility (intraclass correlation, 0.88–0.98; $P < .001$) and good interstudy reproducibility (intraclass correlation, 0.44–0.82; (P value range, .02 to $< .001$) (19,20).

LACI Definition

The LACI was defined for each participant by the ratio between the LA end-diastolic volume and the LV end-diastolic volume assessed at cardiac MRI (T.P., with 5 years of experience). The LV volume was measured from the stack of short-axis cine images, whereas the LA volume was measured from the two- and four-chamber views, as described previously (Fig 2). The LA and LV volumes were measured in the same end-diastolic phase defined by mitral valve closure.

The LACI value is expressed as a percentage, and a higher LACI indicates greater disproportion between the LA and LV volumes at ventricular end-diastole, which reflects greater impairment of left atrioventricular coupling. Moreover, the Δ LACI is defined by the annual difference in the LACI value measured at baseline, at examination 1 and the LACI value measured after 10 years at examination 5 ($LACI_{10}$), and the Δ LACI value is expressed as a percentage per year.

Incident AF

Incident AF during the follow-up period was defined on the basis of study electrocardiograms and hospital discharge diagnosis *International Classification of Diseases–9* codes, supplemented by Medicare claims (Appendix E4 [online]).

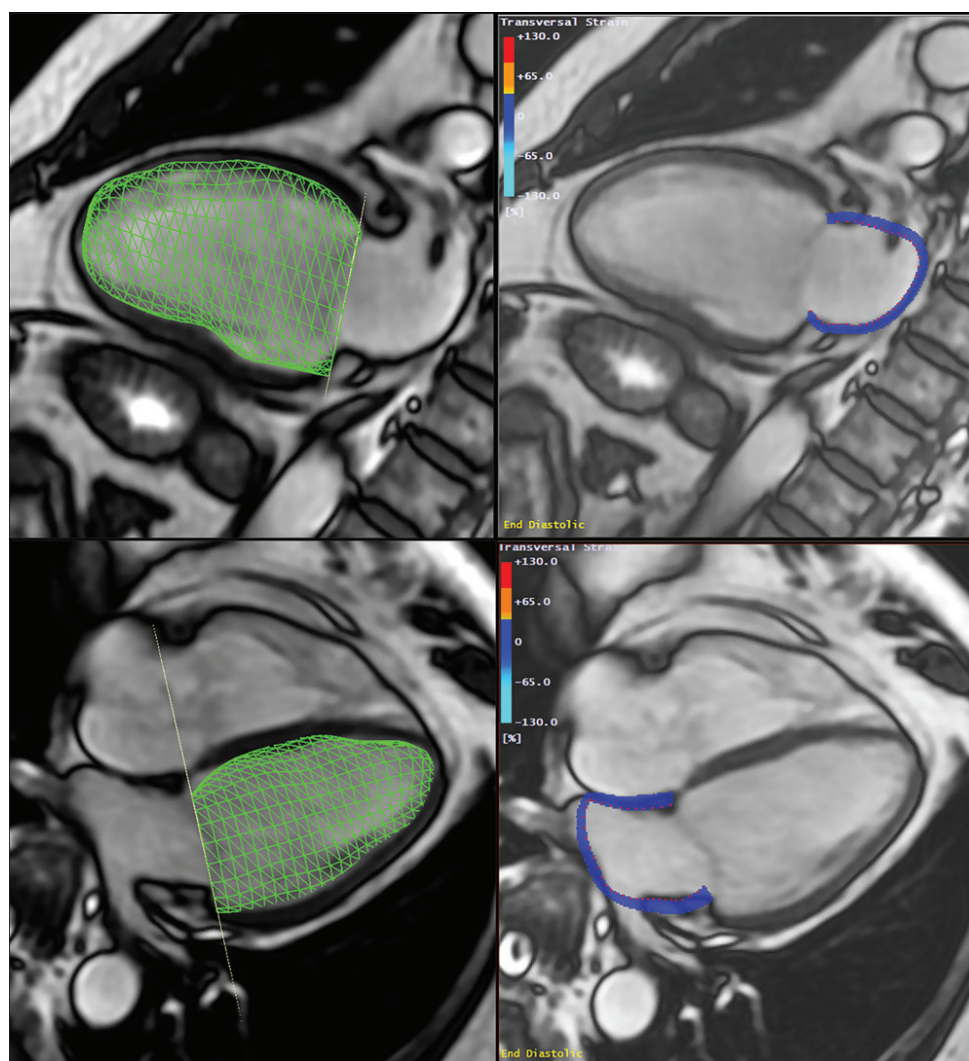


Figure 2: Method to assess the left atrioventricular coupling index (LACI) at cardiac MRI. LACI was defined by the ratio between the left atrial (LA) end-diastolic volume and the left ventricular (LV) end-diastolic volume. A stack of short-axis noncontrast cine MRI scans were acquired to encompass both ventricles, and LV end-diastolic volume was measured by using cardiac image modeler software (green volume, left panel). LA end-diastolic volume was measured by using multimodality tissue-tracking software to track LA wall motion during the end-diastole in the four-chamber and two-chamber views (pink borders, right panel).

Statistical Analysis

Participant characteristics at baseline and after 10 years are presented as means for continuous variables and as counts and percentages for categorical variables (Table 1). Comparisons used the χ^2 or Fisher exact test for categorical variables and the Student t test or Mann-Whitney Wilcoxon test, as appropriate, for continuous variables. We used Cox regression models to study the associations between the LACI, or Δ LACI, and the incident AF. The cumulative risk of incident AF over the follow-up years for the cohort, stratified by the LACI tertiles, or Δ LACI tertiles, was determined by using Kaplan-Meier curves.

The AF risk prediction model used was the Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation (CHARGE-AF) risk model (21). Two models were proposed. In model 1, we adjusted for the following CHARGE-AF risk factors at the second cardiac MRI examination after 10 years (ie, examination 5): age, sex, ethnicity, height, weight, systolic and diastolic blood pressure, use of

Table 1: Characteristics of Participants at Baseline and at Second Examination

Parameters	Baseline (Examination 1) (n = 1911)	Second Study (Examination 5)*		
		No AF (n = 1824)	AF (n = 87)	P Value
Age (y)	59 ± 9	68 ± 9	75 ± 7	<.001
Men	907 (47.5)	860 (47.1)	47 (54.0)	.25
Ethnicity (%)				.04
White	43	42	55	
Chinese American	11	12	5	
African American	25	25	23	
Hispanic	21	21	16	
Hypertension	689 (36.1)	1011 (54.6)	69 (72.6)	.001
Systolic blood pressure (mm Hg)	123 ± 20	122 ± 20	126 ± 21	.16
Diastolic blood pressure (mm Hg)	72 ± 10	68 ± 10	67 ± 11	.17
Hypertension medication	568 (29.7)	908 (49.8)	62 (71.3)	<.001
Body mass index (kg/m ²)	27.8 ± 4.9	28.0 ± 5.1	28.3 ± 5.1	.57
Glycemic status				.21
Normal	1533 (80.2)	1161 (63.7)	48 (55.2)	
Impaired fasting glucose	212 (11.1)	371 (20.3)	22 (25.3)	
Diabetes mellitus	166 (8.7)	292 (16.0)	17 (19.5)	
Smoking status				.003
Never	982 (51.4)	835 (45.8)	24 (27.6)	
Former	699 (36.6)	844 (46.3)	55 (63.2)	
Current	230 (12.0)	144 (7.9)	8 (9.2)	
Heart rate (beats/min)	62 ± 8.6	63.4 ± 9.8	64.5 ± 11.8	.35
CHARGE-AF score (%)	11.6 ± 1.1	12.6 ± 1.2	13.5 ± 0.8	<.001
Cardiovascular events				
Myocardial infarction	0 (0)	25 (1.4)	3 (3.5)	.050
Congestive heart failure	0 (0)	14 (0.8)	3 (3.5)	.054
LA parameters				
LAVI _{min} (mL/m ²)	11.9 ± 5.8	29.6 ± 14.0	42.0 ± 21.4	<.001
LAVI _{max} (mL/m ²)	29.9 ± 9.1	64.5 ± 20.9	74.1 ± 25.4	<.001
LAVI _{preA} (mL/m ²)	22.0 ± 7.4	49.7 ± 17.9	61.4 ± 23.3	<.001
Peak LA strain (%)	37.4 ± 11.2	31.6 ± 13.0	24.3 ± 11.7	<.001
LV parameters				
LV EDVi (mL/m ²)	70.2 ± 11.9	64.9 ± 13.6	65.0 ± 14.6	.96
LVEF (%)	62.6 ± 5.7	62.1 ± 7.1	60.6 ± 8.6	.11
LV mass index (g/m ²)	64.9 ± 11.8	66.1 ± 13.7	69.2 ± 15.7	.06
LV MVR (g/mL)	0.93 ± 0.16	1.04 ± 0.22	1.11 ± 0.26	.02
LACI (%)	16.8 ± 7.9	25.0 ± 11.0	35.8 ± 19.3	<.001

Note.—Unless otherwise indicated, data are number of participants; data in parentheses are percentages. Mean data are ± standard deviation. There were 1911 participants total. AF = atrial fibrillation, CHARGE-AF = Cohorts for Heart and Aging Research in Genomic Epidemiology Model for Atrial Fibrillation, EDVi = end-diastolic volume index, LA = left atrium, LACI = left atrioventricular coupling index, LAVI = left atrium volume index, LAVI_{max} = maximum LAVI, LAVI_{min} = minimum LAVI, LAVI_{preA} = preatrial LAVI, LV = left ventricle, LVEF = left ventricle ejection fraction, MVR = mass-to-volume ratio.

*The second study took place 9.6 years ± 0.4 after baseline.

antihypertensive medication, smoking status, diabetes, and the development of myocardial infarction and congestive heart failure (21). Model 2 included model 1 and the baseline value of the parameter assessed, measured for baseline differences when measuring change (22). The additional predictive value of the LACI and ΔLACI was calculated by the area under receiver operating characteristic curve increment compared with the CHARGE-AF score (21) and each LA or LV parameter. A two-tailed P value less than .05 was considered to indicate statistical significance. All data were analyzed (T.P.

and C.O.W., with 25 years of experience) by using software (R version 3.6.1; R Project for Statistical Computing).

Results

Characteristics of Participants in MESA

Of the 4859 participants with baseline cardiac MRI records that included LA volume assessment (examination 1), 1911 participants (39.3%) returned to undergo a second cardiac MRI examination at examination 5 with LA, LV, and outcome

Table 2: Univariable and Multivariable Analyses of Incident Atrial Fibrillation according to Left Atrioventricular Coupling Index and Other Left Atrial or Left Ventricular Parameters at Examination 5

Parameter	Univariable Analysis		Multivariable Analysis: Model 1*	
	Hazard Ratio	P Value	Hazard Ratio	P Value
LACI ₁₀ [†]	1.82 (1.61, 2.05)	<.001	1.69 (1.46, 1.96)	<.001
LACI ₁₀ cutoff > 30% [‡]	2.62 (1.72, 4.00)	<.001	1.91 (1.23, 2.95)	.004
LAVI _{preA}	1.70 (1.45, 1.99)	<.001	1.52 (1.25, 1.84)	<.001
LAVI _{min}	1.56 (1.42, 1.72)	<.001	1.58 (1.39, 1.79)	<.001
LAVI _{max}	1.46 (1.26, 1.71)	<.001	1.43 (1.20, 1.72)	<.001
Total LAEF	0.41 (0.34, 0.50)	<.001	0.55 (0.46, 0.67)	<.001
Passive LAEF	0.48 (0.38, 0.60)	<.001	0.63 (0.49, 0.83)	<.001
Active LAEF	0.45 (0.36, 0.57)	<.001	0.58 (0.48, 0.71)	<.001
Peak LA strain	0.41 (0.30, 0.57)	<.001	0.62 (0.47, 0.83)	<.001
LV EDVi	1.00 (0.81, 1.24)	.99	1.08 (0.88, 1.33)	.47
LVEF	0.79 (0.65, 0.97)	.02	0.81 (0.66, 1.00)	.06
LV MVR	1.28 (1.07, 1.54)	.008	1.07 (0.86, 1.32)	.56

Note.—All left ventricular (LV) parameters, left atrial (LA) parameters, and left atrioventricular coupling index (LACI) values were normalized according to the following formula: (parameter–mean value)/standard deviation. EDVi = end-diastolic volume index, LACI₁₀ = LACI value measured after 10 years, LAEF = left atrial emptying fraction, LAVI = left atrium volume index, LAVI_{max} = maximum LAVI, LAVI_{min} = minimum LAVI, LAVI_{preA} = preatrial LAVI, LVEF = LV ejection fraction, MVR = mass-to-volume ratio.

* Multivariable model 1 (Cohorts for Heart and Aging Research in Genomic Epidemiology Model for Atrial Fibrillation, or CHARGE-AF, risk model) included the following: age, sex, ethnicity, height, weight, systolic and diastolic blood pressure, antihypertensive medication use, smoking status, diabetes, and the development of myocardial infarction and congestive heart failure. Of note, each row corresponds to a final model including model 1 and we added each of the other parameters one by one, where the *P* value and hazard ratio reflect only the addition of the one additional parameter listed.

[†] LACI₁₀ used as continuous variable.

[‡] LACI₁₀ used as binary variable defined by a cutoff greater than 30%.

data available after a mean time of 9.6 years \pm 0.4 (standard deviation; mean age, 59 years \pm 9; 907 men) (Fig 1). Among the 1911 patients who underwent a second cardiac examination at examination 5, 689 (36.1%) had hypertension with 568 (29.7%) administered antihypertensive therapy, 166 (8.7%) had diabetes mellitus, 230 (12.0%) were current smokers, and mean body mass index was 27.8 kg/m² \pm 4.9. The baseline characteristics of the study population at examination 5 after a mean time of 9.6 years \pm 0.4, divided into those who developed AF or who did not, are presented in Table 1. After a mean follow-up time of 3.9 years \pm 0.9 after the second cardiac MRI examination (examination 5), 87 participants developed incident AF. LA functional parameters were lower, and LV mass and LV volume was higher in participants with AF compared with those without AF.

LACI and Annualized Change in LACI

For the entire study sample, mean baseline LACI was 16.8% \pm 7.9. At follow up, LACI₁₀ was 25.5% \pm 11.2 (mean Δ LACI, 1.2% \pm 1.0 per year; Fig E1 [online]). Δ LACI and individual LA and LV parameters during 9.6 years \pm 0.4 are shown in Table E2 (online). Whereas participants who developed AF had greater increase in LA volume (minimum Δ LAVI, 0.90 mL/m² per year \pm 1.07 vs 0.45 mL/m² per year \pm 0.76; *P* < .001) versus those who did not, LV end-diastolic volumes decreased similarly with aging in both groups (–0.59 mL/m² per year \pm 1.43 vs –0.65 mL/m² per year \pm 1.21; *P* = .70). Correlations between LA and LV end-diastolic volumes were low at both baseline and follow up (*R*² = 0.15 and 0.10, respectively; both *P* < .001; Fig E2 [online]).

We found no evidence of a difference in mean LACI between women and men at baseline (LACI at baseline, 16.7% \pm 8.3 vs 16.9% \pm 7.5, respectively; *P* = .46). However, at follow up, mean LACI was higher in women than in men (LACI₁₀, 26.2% \pm 12.2 vs 24.8% \pm 11.4, respectively; *P* = .01). Consistently, Δ LACI was higher in women than in men (1.01% per year \pm 1.20 vs 0.84% per year \pm 1.18, respectively; *P* = .002; Table E3 [online]).

LACI and Incident AF

The results of unadjusted and adjusted Cox proportional hazard models for LACI₁₀ and LA and LV parameters measured after 10 years are in Table 2. LACI₁₀ was positively associated with incident AF before and after adjustment for risk factors (adjusted hazard ratio [HR], 1.69; 95% CI: 1.46, 1.96; increment by 1 standard deviation; *P* < .001). LACI₁₀ top tercile (LACI₁₀ > 28.6%) was more strongly associated with AF incidence than the bottom tercile (<19.7%; log-rank *P* < .001; Fig 3A). By using an optimal cutoff point to predict incident AF (Fig E3 [online]), LACI₁₀ greater than 30% was independently associated with incident AF before (HR, 2.62; 95% CI: 1.72, 4.00; *P* < .001) and after adjustment (adjusted HR, 1.91; 95% CI: 1.23, 2.95; *P* = .004; Fig 3B). LACI value at baseline measured at examination 1 was also independently associated with AF (HR, 1.81; 95% CI: 1.57, 2.01; *P* < .001; Table E4 [online]).

Annualized Change in LACI and Incident AF

Table 3 shows the results of bivariate and multivariable analyses for Δ LACI and main LA and LV parameters; unadjusted results are shown in Table E5 (online).

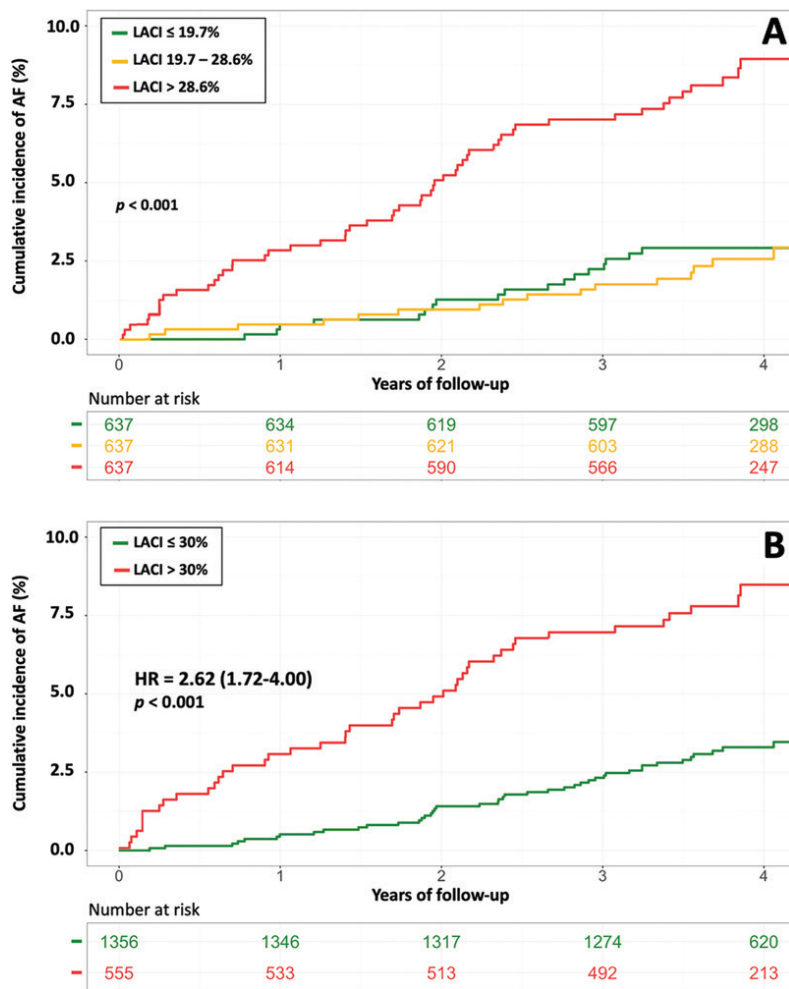


Figure 3: Kaplan-Meier survival curves for incident atrial fibrillation (AF) stratified by **(A)** left atrioventricular coupling index (LACI) tertiles and by **(B)** a LACI cutoff of 30%. **(A)** The cumulative hazard was greater in the third LACI value measured after 10 years (LACI₁₀) tertile compared with the first tertile for incident AF (hazard ratio [HR], 2.48; 95% CI: 1.53, 3.87; *P* < .001). **(B)** The cumulative hazard was greater for participants with LACI₁₀ greater than 30% compared with participants with LACI₁₀ of 30% or less for incident AF (HR, 2.62; 95% CI: 1.72, 4.00; *P* < .001).

Annual change in LACI was positively associated with AF before and after adjustment (LACI value at baseline HR, 1.76 [95% CI: 1.55, 2.00] and 1.79 [95% CI: 1.60, 2.01], respectively; both *P* < .001). After adjusting for CHARGE-AF risk factors (model 1) and LACI value at baseline (model 2), Δ LACI remained independently associated with incident AF (adjusted model 1 HR, 1.64 [95% CI: 1.42, 1.89] per 1 standard deviation increment; adjusted model 2 HR, 1.71 [95% CI: 1.50, 1.94] per 1 standard deviation increment; both *P* < .001). The top tertile (>1.3% per year) of Δ LACI was more strongly associated with incident AF than the bottom tertile (<0.4% per year; log-rank *P* < .001; Fig 4A).

By using an optimal Δ LACI cutoff value greater than 1.5% per year to predict incident AF (Fig E4 [online]), an increase in Δ LACI greater than 1.5% per year remained independently associated with greater AF occurrence (adjusted model 1 HR, 2.55 [95% CI: 1.75, 3.72] per 1 standard deviation increment; adjusted model 2 HR, 3.25 [95% CI: 2.20, 4.82] per 1 standard deviation increment; both

P < .001) (Fig 4B). In participants with LACI₁₀ greater than 30%, the cumulative hazard was greater for participants with Δ LACI greater than 1.5% per year than for those with Δ LACI less than or equal to 1.5% per year (*P* < .001). However, among participants with LACI₁₀ less than or equal to 30%, we found no evidence of differences between those with Δ LACI greater or less than 1.5% per year (*P* = .46) (Fig 5).

Atrioventricular Coupling Improvement of AF Risk Prediction

The multivariable model with the LACI₁₀ showed improvement in model discrimination compared with the multivariable model with CHARGE-AF risk factors for predicting incident AF (area under receiver operating characteristic curve, 0.78 vs 0.74, respectively; *P* < .001). Follow-up examination LACI₁₀ also showed better discrimination for incident AF than the multivariable model with individual LA or LV parameter and the CHARGE-AF score risk factors (Table 4).

Improvement in Risk Prediction with Addition of Average Annualized Change in LACI

After adjustment, Δ LACI showed improvement in model discrimination compared with the multivariable model with CHARGE-AF risk factors for predicting incident AF (area under receiver operating characteristic curve, 0.80 vs 0.74, respectively; *P* < .001). Δ LACI also showed better discrimination for incident AF than did the multivariable model with average annualized changes in LA or LV parameters (Table 5).

Discussion

In our study, we demonstrated the predictive value of both a left atrioventricular coupling index (LACI) and the average annualized change in LACI (Δ LACI) for predicting incident atrial fibrillation (AF) in a multiethnic population free of clinical cardiovascular disease at enrollment. LACI and Δ LACI showed strong associations with incident AF (hazard ratio [HR] for both, 1.7; *P* < .001). Moreover, LACI and Δ LACI were stronger independent predictors of incident AF than the Cohort for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation (CHARGE-AF) score and individual left atrial (LA) or left ventricular (LV) parameters, resulting in improved discrimination for incident AF (area under receiver operating characteristic curve, 0.78 vs 0.74, respectively; and area under receiver operating characteristic curve, 0.80 vs 0.74, respectively; both *P* < .001). The increase in LA volume relative to that of the LV at end-diastole reflects impaired LV compliance, leading to a reduction of LA reservoir function, which were independent predictors of incident AF (23). We also investigated the best LACI and Δ LACI cutoff points to predict incident AF and found that LACI greater than 30% and Δ LACI greater than 1.5% per year were independently associated with

Table 3: Bivariate and Multivariable Analyses of Incident Atrial Fibrillation according to Annual Change in Left Atrioventricular Coupling Index and Annual Change in Other Left Atrial or Left Ventricular Parameters

Parameter	Bivariate Analysis*		Model 1†		Model 2‡	
	Hazard Ratio	P Value	Hazard Ratio	P Value	Hazard Ratio	P Value
ΔLACI§	1.79 (1.60, 2.01)	<.001	1.64 (1.42, 1.89)	<.001	1.71 (1.50, 1.94)	<.001
ΔLACI cutoff > 1.5%/year	4.01 (2.75, 5.85)	<.001	2.55 (1.75, 3.72)	<.001	3.25 (2.20, 4.82)	<.001
ΔLAVI _{preA}	1.54 (1.30, 1.82)	<.001	1.30 (1.09, 1.56)	.003	1.44 (1.21, 1.71)	<.001
ΔLAVI _{min}	1.57 (1.44, 1.73)	<.001	1.58 (1.39, 1.79)	<.01	1.62 (1.45, 1.82)	<.001
ΔLAVI _{max}	1.37 (1.15, 1.63)	<.001	1.20 (1.00, 1.44)	.044	1.34 (1.10, 1.63)	.004
ΔTotal LAEF	0.40 (0.32, 0.49)	<.001	0.72 (0.6, 0.86)	.003	0.44 (0.33, 0.57)	<.001
ΔPassive LAEF	0.40 (0.31, 0.52)	<.001	0.91 (0.74, 1.11)	.35	0.54 (0.40, 0.72)	<.001
ΔActive LAEF	0.45 (0.35, 0.57)	<.001	0.74 (0.61, 0.89)	.002	0.47 (0.36, 0.61)	<.001
ΔPeak LA strain	0.44 (0.34, 0.56)	<.001	0.80 (0.66, 0.97)	.02	0.57 (0.42, 0.77)	<.001
ΔLV EDVi	0.95 (0.78, 1.16)	.62	1.03 (0.88, 1.22)	.68	1.04 (0.87, 1.25)	.64
ΔLVEF	0.92 (0.75, 1.13)	.44	1.04 (0.88, 1.24)	.65	0.96 (0.79, 1.17)	.68
ΔLV MVR	1.28 (1.08, 1.52)	.005	1.05 (0.9, 1.24)	.52	1.11 (0.89, 1.37)	.36

Note.—All variables were expressed per 1 standard deviation per year and normalized according to the following formula: (variable measured – mean value)/standard deviation. Data in parentheses are 95% CIs. Each cell corresponds to a final model including model 1 or 2 and we added each of the other annual change in parameters one by one, wherein the *P* value and hazard ratio reflect only the addition of the one additional annual change in parameter listed. Δ = annual change, EDVi = end-diastolic volume indexed, LA = left atrial, LAEF = left atrial emptying fraction (%), LACI = left atrioventricular coupling index, LAVI = left atrium volume index, LAVI_{max} = maximum LAVI, LAVI_{min} = minimum LAVI, LAVI_{preA} = preatrial LAVI, LV = left ventricle, LVEF = left ventricle ejection fraction, MVR = mass-to-volume ratio.

* Bivariate model included both the annual change in the variable and the value of the variable measured at baseline.

† Multivariable model 1 (Cohorts for Heart and Aging Research in Genomic Epidemiology Model for Atrial Fibrillation, or CHARGE-AF risk model) included the following: age, sex, ethnicity, height, weight, systolic and diastolic blood pressure, antihypertensive medication use, smoking status, diabetes, and the development of myocardial infarction and congestive heart failure.

‡ Multivariable model 2 included the following: model 1 and baseline value measured at examination 1 for each LA or LV parameter.

§ Annual change in LACI used as continuous variable.

|| Annual change in LACI used as binary variable defined by a cutoff greater than 1.5% per year.

incident AF (HR 1.91 and HR 3.25, both *P* < .001). Interestingly, the occurrence of AF was higher for participants with a ΔLACI greater than 1.5% per year than for participants with a ΔLACI less than or equal to 1.5% per year among participants with a LACI greater than 30% (8.8% vs 3.8%, respectively; *P* < .001). However, among participants with LACI less than or equal to 30%, we found no evidence of no differences between those with ΔLACI greater than 1.5% per year versus those with ΔLACI less than or equal to 1.5% per year (2.5% vs 1.3%; *P* = .46). Whereas the Multi-Ethnic Study of Atherosclerosis showed the excellent prognostic value of CHARGE-AF score (24), our results suggest that the assessment of LACI and ΔLACI provides additional and relevant information to accurately stratify the risk of incident AF above CHARGE-AF risk factors in a population without known cardiovascular disease.

A previous report (7) suggested that adverse LA remodeling facilitates both initiation and maintenance of AF by promoting ectopic triggers and altering the wavelength of the re-entrant arrhythmic circuit. Knowing the crucial role of cardiac MRI data in predicting AF (25), LACI appears to reflect an earlier stage of LA remodeling than individual LA parameters, with stronger prognostic value for predicting incident AF before and after adjustment for traditional risk factors. In line with previous reports (8,10,11), these results suggest that AF may not occur

exclusively because of impaired LA or LV structure or function but may also be susceptible to uncoupling of LA and LV structure and function as markers of early LV diastolic dysfunction or early LA myopathy.

Our findings are also consistent with those of previous echocardiography studies that assessed left atrioventricular coupling (26,27), and those of a previous cardiac MRI study performed in 40 healthy individuals that investigated the effects of aging on left atrioventricular coupling and LV filling (28). In that study, older individuals had larger LA and smaller LV volumes with larger LA-to-LV end-diastolic volume ratios (27% ± 6 vs 19% ± 3, respectively; *P* < .001) and preserved LV ejection fraction. Moreover, in a canine model of early-stage hypertensive heart failure with preserved LV ejection fraction, left heart atrioventricular coupling assessed at cardiac MRI was impaired, and the curvilinear LA end-reservoir pressure-volume relationship was shifted upward and leftward, indicating reduced LA compliance (29). A recent study (30) described a LACI measured at echocardiography as a prognosticator of death in patients with heart failure with reduced LV ejection fraction or degenerative mitral disease and regurgitation.

Regarding the optimal time of the cardiac cycle at which the LACI should be assessed, some reports have emphasized the important interaction between LA and LV performance,

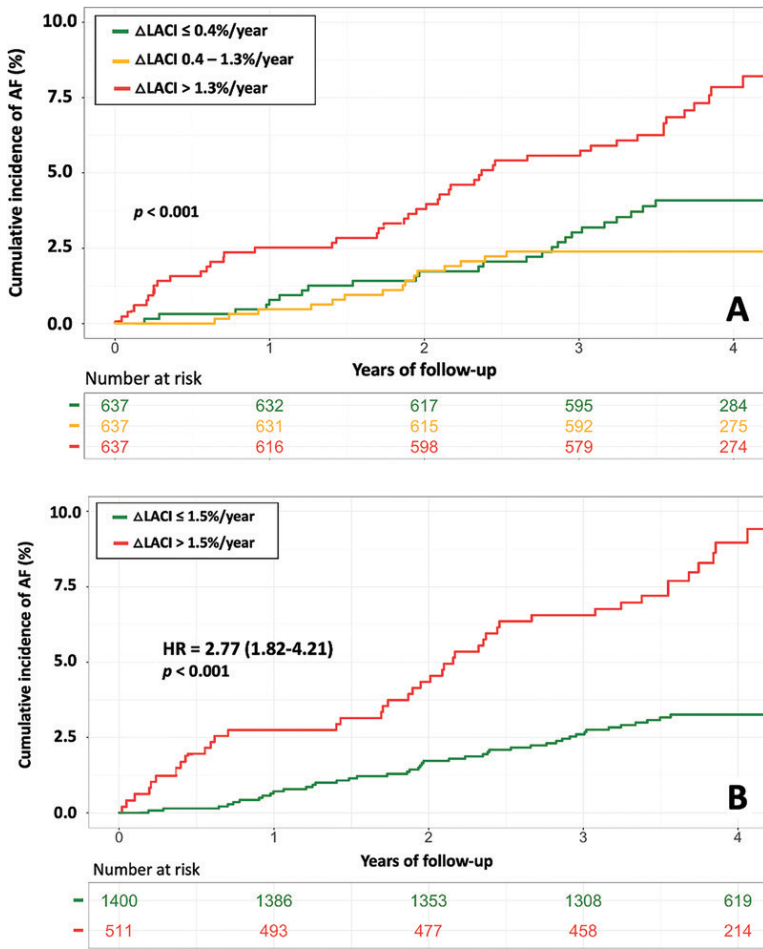


Figure 4: Kaplan-Meier survival curves for incident atrial fibrillation (AF) stratified by tertiles of annual change (Δ) in left atrioventricular coupling index (LACI) (A) and by annual change in LACI with a cutoff of 1.5% per year (B). (A) The cumulative hazard was greater in the third tertile compared with the first tertile for incident AF (hazard ratio [HR], 2.52; 95% CI: 1.57, 3.96; $P < .001$). (B) The cumulative hazard was greater for participants with LACI greater than 1.5% per year compared with participants with annual change in LACI of 1.5% or less per year for incident AF (HR, 2.77; 95% CI: 1.82, 4.21; $P < .001$).

particularly during the LV end diastole (12,13). Furthermore, a recent investigation has suggested that LA end-diastolic volume (31,32) or change in LA end-diastolic volume (14,33) is more closely correlated with diastolic function (13), and therefore more robust than maximal LA volume (at LV end systole) for predicting AF. However, a rise in LA end-diastolic volume (LA minimum volume) has been reported as a strong predictor of AF (14,31), reflecting the hemodynamic interactions between LA and LV during LV diastole (23). Indeed, at the beginning of LV diastole, passive filling begins as a rotating blood flow pattern within the LA, gradually decreasing to a halt when pressures between the two chambers equalize. This passive filling pattern generates an early diastolic blood flow vortex inside the LV that is stronger than the original flow rotational pattern from the LA. The resultant buildup of kinetic energy expands the LV to a greater diastolic volume than it would in the absence of such vortex phenomenon (34). Such mechanisms underlie the important hemodynamic interactions between LA and LV during LV diastole, possibly in part explaining the particular prognostic value of LACI.

Our study had limitations. First, LACI was investigated as a diagnostic tool for early detection of AF risk in asymptomatic participants without known cardiovascular disease. Hence, LACI may not be as an ideal assessment tool for participants with pronounced LA and LV enlargement secondary to advanced structural heart disease. For these reasons, the extension of our findings to populations with established cardiovascular disease requires further investigation, including probably the assessment of another LACI cutoff in these patients. Second, incident AF was on the basis of diagnosis discharge codes, which may underestimate AF incidence because many AF cases can be asymptomatic. Third, Δ LACI was

Figure 5: Kaplan-Meier survival curves for incident atrial fibrillation (AF) stratified simultaneously by left atrioventricular coupling index (LACI) value measured after 10 years ($LACI_{10}$) with a cutoff of 30% and an annual change (Δ) in LACI with a cutoff of 1.5% per year. In participants with a $LACI_{10}$ greater than 30%, the cumulative hazard was greater for participants with annual change in LACI greater than 1.5% per year than for those with annual change LACI of 1.5% or less per year (hazard ratio [HR], 2.20; 95% CI: 1.08, 4.15; $P < .001$). However, among participants with $LACI_{10}$ of 30% or less, we found no evidence of differences between those with annual change in LACI greater than or less than 1.5% per year (HR, 1.19; 95% CI: 0.87, 1.89; $P = .46$).

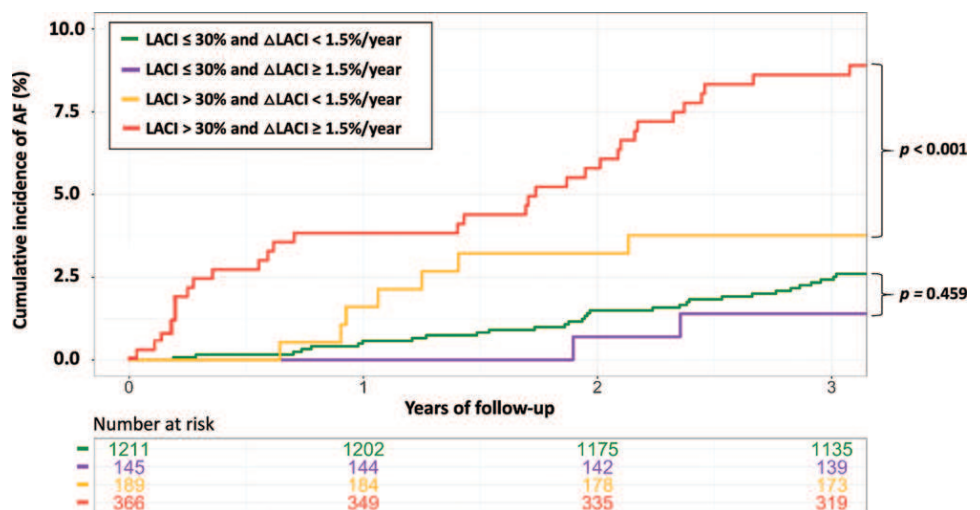


Table 4: Discrimination Associated with Left Atrioventricular Coupling Index to Different Left Atrial and Left Ventricular Parameters at Examination 5 to Predict Incident Atrial Fibrillation

Parameter	AUC Incident Atrial Fibrillation
Model 1	0.74 (0.70, 0.78)
Model 1 and LACI ₁₀ *	0.78 (0.73, 0.83)
Model 1 and LACI ₁₀ cutoff > 30%†	0.77 (0.73, 0.81)
Model 1 and LAVI _{preA}	0.76 (0.71, 0.81)
Model 1 and LAVI _{min}	0.76 (0.72, 0.81)
Model 1 and LAVI _{max}	0.74 (0.70, 0.79)
Model 1 and total LAEF	0.76 (0.72, 0.82)
Model 1 and passive LAEF	0.75 (0.71, 0.80)
Model 1 and active LAEF	0.76 (0.72, 0.81)
Model 1 and peak LA strain	0.75 (0.71, 0.81)
Model 1 and LV EDVi	0.75 (0.71, 0.79)
Model 1 and LVEF	0.75 (0.70, 0.79)
Model 1 and LV MVR	0.74 (0.71, 0.78)

Note.—Data in parentheses are 95% CIs. All left ventricular (LV) parameter, left atrial (LA) parameter, and left atrioventricular coupling index (LACI) values were normalized according to the following formula: (parameter – mean value)/standard deviation. Multivariable model 1 (Cohorts for Heart and Aging Research in Genomic Epidemiology Model for Atrial Fibrillation, or CHARGE-AF, risk model) included the following: age, sex, ethnicity, body mass index, systolic and diastolic blood pressure, antihypertensive medication use, smoking status, diabetes, and the development of myocardial infarction and congestive heart failure. AUC = area under the receiver operating characteristic curve, EDVi = end-diastolic volume index, EF = emptying fractions, LACI₁₀ = LACI value measured after 10 years, LAEF = left atrial emptying fraction, LAVI = left atrium volume index, LAVI_{max} = maximum LAVI, LAVI_{min} = minimum LAVI, LAVI_{preA} = preatrial LAVI, LVEF = left ventricle ejection fraction, MVR = mass-to-volume ratio.

* LACI₁₀ used as continuous variable.

† LACI₁₀ used as binary variable defined by a cutoff greater than 30%.

averaged across 10 years, thus assuming linearity over time. This method may not have fully captured the variation in year-to-year measurements, therefore providing additional precedence for further investigation. Fourth, we used two-dimensional methods instead of three-dimensional methods to measure LA volumes from two-chamber and four-chamber cine MRI, which may have underestimated true volumes by 11.5%–20% (35). Moreover, these LA volumes were performed with only one software program, which limited the generalizability of the findings. Fifth, knowing that cardiovascular MRI is not a widely accessible test in routine, the use of LACI should be investigated in echocardiography, particularly with the advent of three-dimensional echocardiography. Finally, although the mechanisms by which incident AF is associated with left atrioventricular coupling impairment are not entirely elucidated by our observational data, our results may provide valuable clues to AF pathophysiologic structure in human populations.

Table 5: Discrimination Associated with Annual Change in Left Atrioventricular Coupling Index to Change in Different Left Atrial and Left Ventricular Parameters to Predict Incident Atrial Fibrillation

Parameter	AUC Incident Atrial Fibrillation
Model 1	0.74 (0.70, 0.78)
Model 2 and ΔLACI*	0.80 (0.75, 0.84)
Model 2 and ΔLACI cutoff > 1.5% per year†	0.79 (0.75, 0.83)
Model 2 and ΔLAVI _{preA}	0.77 (0.73, 0.82)
Model 2 and ΔLAVI _{min}	0.78 (0.73, 0.82)
Model 2 and ΔLAVI _{max}	0.76 (0.71, 0.80)
Model 2 and Δtotal LAEF	0.78 (0.73, 0.82)
Model 2 and Δpassive LAEF	0.77 (0.73, 0.81)
Model 2 and Δactive LAEF	0.78 (0.73, 0.83)
Model 2 and Δpeak LA strain	0.77 (0.72, 0.81)
Model 2 and ΔLV EDVi	0.74 (0.70, 0.78)
Model 2 and ΔLVEF	0.74 (0.70, 0.78)
Model 2 and ΔLV MVR	0.75 (0.70, 0.79)

Note.—Data in parentheses are 95% CIs. All variables values are expressed per 1 standard deviation per year and normalized according to the following formula: (variable measured – mean value)/standard deviation. Multivariable model 1 (Cohorts for Heart and Aging Research in Genomic Epidemiology Model for Atrial Fibrillation, or CHARGE-AF, risk model) included the following: age, sex, ethnicity, body mass index, systolic and diastolic blood pressure, antihypertensive medication use, smoking status, diabetes, and the development of myocardial infarction and congestive heart failure. Multivariable model 2 included the following: model 1 and baseline value measured at examination 1 for each left atrial or left ventricular parameter. Δ = annual change, AUC = area under the receiver operating characteristic curve, EDVi = end-diastolic volume index, LA = left atrium, LACI = left atrioventricular coupling index, LAEF = left atrial emptying fraction, LAVI = left atrium volume index, LAVI_{max} = maximum LAVI, LAVI_{min} = minimum LAVI, LAVI_{preA} = preatrial LAVI, LV = left ventricle, LVEF = left ventricle ejection fraction, MVR = mass-to-volume ratio.

* ΔLACI used as continuous variable.

† ΔLACI used as binary variable defined by a cutoff greater than 1.5% per year.

In conclusion, in a large multiethnic population (ie, the Multi-Ethnic Study of Atherosclerosis) free of clinical cardiovascular disease at baseline, impaired left atrioventricular coupling reflected as greater left atrioventricular coupling index (LACI) and annualized change in LACI, or ΔLACI, measured at cardiac MRI were associated with higher risk of incident atrial fibrillation (AF) during a 4-year median follow-up. The addition of LACI and ΔLACI to risk prediction models for incident AF improved model discrimination for incident AF risk. Future studies should validate these findings to better understand the role of left atrioventricular coupling in AF pathophysiologic structure and risk prediction.

Author contributions: Guarantors of integrity of entire study, T.P., H.D.d.V., P.H., J.A.C.L.; study concepts/study design or data acquisition or data analysis/interpreta-

tion, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **T.P., B.A.V., H.D.d.V., P.H., D.A.B., J.A.C.L.**; clinical studies, **T.P., B.A.V., H.D.d.V., D.A.B.**; experimental studies, **P.H., J.A.C.L.**; statistical analysis, **T.P., B.A.V., H.D.d.V., C.O.W.**; and manuscript editing, all authors

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Partie 6 :

Étude n°5 : Valeur pronostique du changement annuel du LACI pour prédire le risque d'insuffisance cardiaque

Left Atrioventricular Coupling Index to Predict Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis

Pezel, T ; Ambale Venkatesh B, Kato Y, De Vasconcellos HD, Heckbert SR, Wu CO, Post WS, Bluemke DA, Cohen-Solal A, Henry P, Lima JAC

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Cette cinquième étude s'inscrit dans la continuité de l'étude précédente. En effet, après avoir démontré dans l'étude n°4 la forte valeur pronostique de la variation annuelle sur dix ans de la mesure de notre indice de couplage auriculo-ventriculaire gauche, le LACI, pour prédire le risque de fibrillation atriale, nous allons dans cette étude n°5 évaluer l'intérêt pronostique de la variation annuelle du LACI en termes de prédiction du risque d'insuffisance cardiaque.

Ainsi, l'objectif de cette nouvelle étude était d'étudier la valeur pronostique d'un indice de couplage auriculo-ventriculaire gauche (LACI), mesuré par IRM cardiaque, ainsi que sa variation annuelle pour prédire le risque d'insuffisance cardiaque dans l'étude MESA.

Dans l'étude MESA, 2 250 participants à l'étude, exempts d'insuffisance cardiaque et de maladies cardiovasculaires au départ, ont eu une mesure du LACI évaluée par IRM cardiaque au départ (examen 1, 2000-2002) et 10 ans plus tard (examen 5, 2010-2012). Le LACI a été défini comme le rapport des volumes télédiastoliques de l'oreillette gauche et du ventricule gauche. Des modèles de risque proportionnel de Cox univariés et multivariés ont été utilisés pour évaluer les associations du LACI et de sa variation annualisée moyenne avec l'insuffisance cardiaque après ajustement pour les facteurs de risque traditionnels. La prédiction du risque supplémentaire a été calculée à l'aide de la statistique C, de l'indice de reclassement net catégoriel (NRI) et de l'indice de discrimination intégrative (IDI).

Parmi les 2 250 participants (âge moyen 59 ± 9 ans et 48 % de participants masculins), 50 événements d'insuffisance cardiaque se sont produits plus de $6,8 \pm 1,3$ ans après le deuxième examen d'IRM cardiaque. Après ajustement, la valeur du LACI et de sa variation annualisée moyenne étaient indépendamment associés à la survenue d'insuffisance cardiaque (HR ajusté 1,44, IC à 95 % [1,25–1,66] et HR ajusté 1,55, IC à 95 % [1,30–1,85], respectivement ; les deux $p < 0,0001$). En utilisant les modèles ajustés, le LACI a montré une amélioration significative de la discrimination et de la reclassification des modèles par rapport au modèle de score de risque d'insuffisance cardiaque actuellement utilisé pour prédire le risque d'insuffisance cardiaque (statistique C : 0,81 contre 0,77 ; NRI = 0,411 ; IDI = 0,043). De façon similaire et après ajustement, la variation annualisée moyenne du LACI a également montré une amélioration significative de la discrimination du modèle par rapport au modèle multivarié avec des facteurs de risque traditionnels pour prédire l'insuffisance cardiaque (C-statistique : 0,82 contre 0,77 ; NRI = 0,491 ; IDI = 0,058).

En résumé, dans cette étude n°5 incluant des patients âgés de 45 à 84 ans sans maladie cardiovasculaire à l'inclusion de l'étude MESA, nos résultats suggèrent la forte et

indépendante valeur pronostique du LACI et de sa variation annualisée moyenne, pour prédire le risque de développer une insuffisance cardiaque. De plus, le LACI et sa variation annualisée moyenne permettaient de donner une amélioration significative de la discrimination et de la reclassification du modèle finale au-delà des facteurs de risque traditionnels connus de la littérature. À notre connaissance, cette étude est la première à décrire l'intérêt de la mesure d'un indice de couplage auriculo-ventriculaire gauche et de sa variation annualisée moyenne pour stratifier le risque de développer une insuffisance cardiaque.



Left Atrioventricular Coupling Index to Predict Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis

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Background: Although left atrial (LA) and left ventricular (LV) structural and functional parameters have independent prognostic value as predictors of heart failure (HF), the close physiological relationship between the LA and LV suggest that the assessment of LA/LV coupling could better reflect left atrioventricular dysfunction and be a better predictor of HF.

Aim: We investigated the prognostic value of a left atrioventricular coupling index (LACI), measured by cardiovascular magnetic resonance (CMR), as well as change in LACI to predict incident HF in the Multi-Ethnic Study of Atherosclerosis (MESA).

Materials and Methods: In the MESA, 2,250 study participants, free of clinically recognized HF and cardiovascular disease (CVD) at baseline, had LACI assessed by CMR imaging at baseline (Exam 1, 2000–2002), and 10 years later (Exam 5, 2010–2012). Left atrioventricular coupling index was defined as the ratio of LA to LV end-diastolic volumes. Univariable and multivariable Cox proportional hazard models were used to evaluate the associations of LACI and average annualized change in LACI (Δ LACI) with incident HF after adjustment for traditional MESA-HF risk factors. The incremental risk prediction was calculated using C-statistic, categorical net reclassification index (NRI) and integrative discrimination index (IDI).

Results: Among the 2,250 participants (mean age 59.3 ± 9.3 years and 47.6% male participants), 50 incident HF events occurred over 6.8 ± 1.3 years after the second CMR exam. After adjustment, greater LACI and Δ LACI were independently associated with HF (adjusted HR 1.44, 95% CI [1.25–1.66] and adjusted HR 1.55, 95% CI [1.30–1.85], respectively; both $p < 0.0001$). Adjusted models for LACI showed significant improvement in model discrimination and reclassification compared to currently used HF risk score model for predicting HF incidence (C-statistic: 0.81 vs. 0.77; NRI = 0.411; IDI = 0.043). After adjustment, Δ LACI showed also significant improvement in model discrimination compared to the multivariable model with traditional MESA-HF risk factors for predicting incident HF (C-statistic: 0.82 vs. 0.77; NRI = 0.491; IDI = 0.058).

Conclusions: In a multi-ethnic population, atrioventricular coupling (LACI), and coupling change (Δ LACI) are independently associated with incident HF. Both have incremental prognostic value for predicting HF events over traditional HF risk factors.

Keywords: heart failure, cardiac magnetic resonance image, coupling, prognosis, left atria, left ventricle, multi-ethnic study of atherosclerosis

INTRODUCTION

Heart failure (HF) is a leading cause of mortality worldwide and a major public health issue especially in older individuals (1). The prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to $\geq 10\%$ among people >70 years of age (1, 2). Given the important medico-economic burden associated with HF, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines reclassified HF to include stage A which includes individuals with risk factors but no structural heart disease (3). Therefore, early detection of these high-risk individuals is imperative for primary prevention. To address the need for early detection of individuals at risk for HF, several studies have assessed left atrial (LA) and left ventricular (LV) structure and function by cardiovascular magnetic resonance (CMR) (4). Several LV structural and functional parameters, such as left ventricular ejection fraction (LVEF), LV mass index, LV mass to volume ratio (LVMVR), or LV global function index (LVGFI) have shown prognostic value in predicting the occurrence of HF (5–8). However, many studies emphasize the fact that HF does not occur exclusively because of impaired LV structure and function (9, 10). Left atrial structural and functional parameters, such as LA volumes and peak LA reservoir strain have been established as an independent predictors of HF (9, 11, 12). Therefore, even with preserved LV systolic function, LA dysfunction may impair global heart performance and uncoupling between functional performance of the two chambers can also contribute to cardiac dysfunction and HF (13). These findings suggest that the LA parameters could allow earlier detection of HF risk than LV parameters. Interestingly, a study using speckle-tracking by echocardiography recently suggested a potential interest of a global atrioventricular strain in asymptomatic individuals with subclinical heart dysfunction beyond the isolated use of the LA or LV strain (14). In line with these findings, although LV and LA parameters have independent prognostic values for predicting HF, the inherently connected physiological relationship between the LA and the LV (15, 16) suggests that the assessment of left atrioventricular coupling alterations could better reflect left heart dysfunction (17). Indeed, our working group has recently demonstrated the prognostic value of a novel left atrioventricular

coupling index (LACI), defined by the ratio of the LA end-diastolic volume divided by the LV end-diastolic volume by CMR, the increase of which is independently associated with cardiovascular events in MESA (18).

Previous studies have also shown the superiority of longitudinal evaluations of change in LA and LV parameters to predict HF (19–21). Therefore, we theorized that longitudinal assessment of atrioventricular coupling could be complementary to the cross-sectional evaluation to stratify the risk of incident HF among healthy individuals. Based on this rationale, we designed an analysis to examine the associations of the LACI and change in LACI with incident HF in a prospective population study of individuals without a history of clinical heart disease at baseline. Specifically, we aim to investigate the prognostic value of LACI and the average annualized change in LACI (Δ LACI) measured by CMR, for predicting incident HF in the Multi-Ethnic Study of Atherosclerosis (MESA).

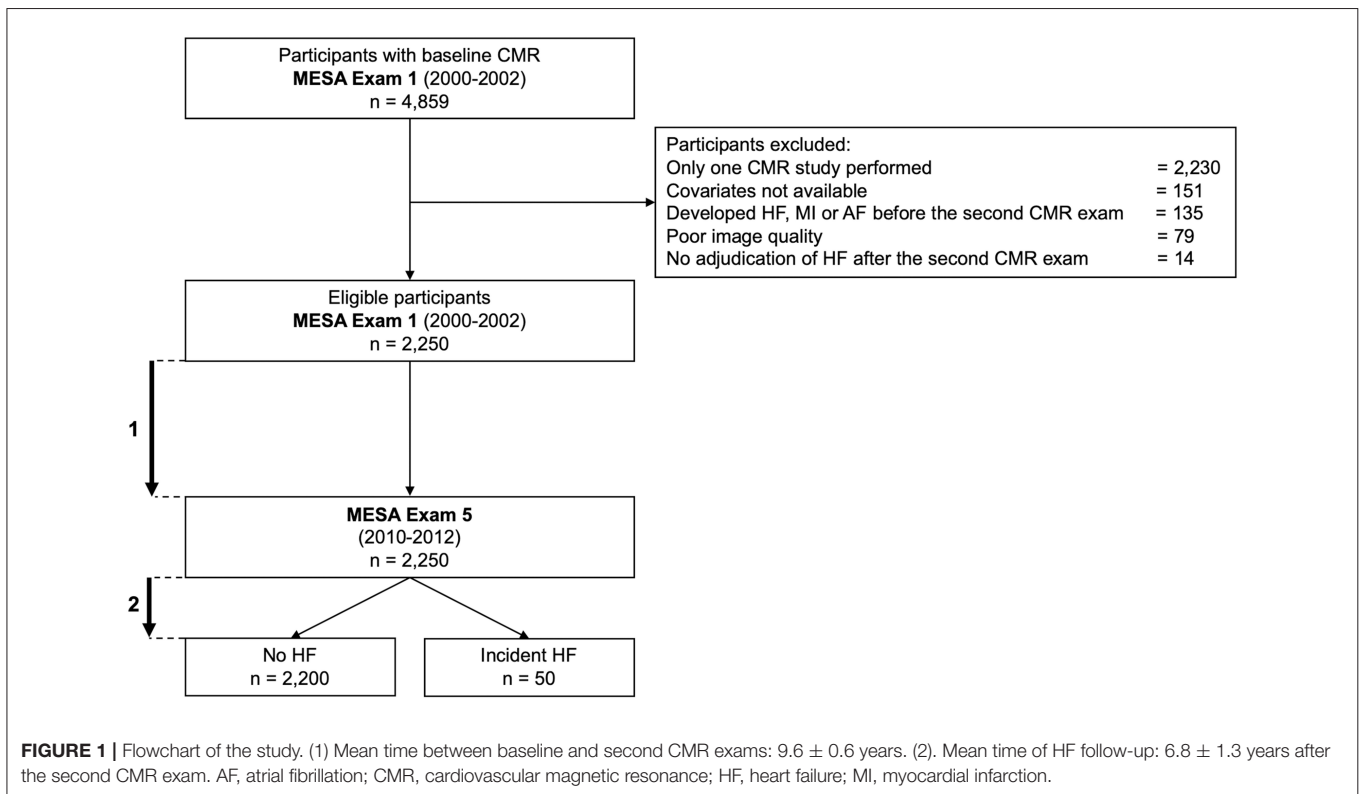
MATERIALS AND METHODS

Study Population

The MESA is a prospective, population-based multi-ethnic (White, African American, Chinese, and Hispanic) cohort study of subclinical cardiovascular disease (CVD). The details of the study design was previously described (22). In summary, between 2000 and 2002 (Exam 1), 6,814 men and women aged from 45 to 84 years, free of clinical CVD at enrollment, were recruited from six US field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and St Paul, MN). Exam 1 was followed by Exam 2 (2002–2004), Exam 3 (2004–2005), Exam 4 (2005–2007), and Exam 5 (2010–2012). Participants with cardiovascular risk factors were not excluded. Participants with any significant valvular disease (stenosis or regurgitation) at baseline were excluded. The methodology of baseline characteristics and outcome collection is detailed in **Supplementary File 1**. All participants provided written informed consent. All study protocols were approved by the institutional review boards of each participating field center.

A flowchart of the MESA population investigated in the current study is depicted in **Figure 1**. Participants were excluded if: (i) they did not have the second CMR exam, (ii) their images were missing or not of sufficient quality to allow measurement of LA and LV volumes, or (iii) they developed incident HF, myocardial infarction, or atrial fibrillation, including patients who had HF during AF, between Exam 1 and Exam 5 (**Figure 1**). Of note, incident HF between Exam 1 and Exam 5 was defined as any episode of acute HF irrespective of its etiology, including acute HF secondary to other cardiac conditions. Of the

Abbreviations: CMR, cardiovascular magnetic resonance; CVD, cardiovascular disease; HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; LVMVR, LV mass to volume ratio; LA, left atrium; LACI, left atrioventricular coupling index; LACI_{Baseline}, left atrioventricular coupling index measured at baseline (MESA Exam 1); LACI_{10-years}, left atrioventricular coupling index measured after 10-years (MESA Exam 5); Δ LACI, average annualized change in left atrioventricular coupling index; MESA, multi-ethnic study of atherosclerosis.



4,859 participants with baseline CMR that included LA volume assessment (Exam 1), 2,250 participants returned for a second CMR exam at Exam 5 after a mean time of 9.6 ± 0.6 years and were included in the study.

CMR Protocol and Image Analysis

Cardiovascular magnetic resonance was performed with 1.5 T MR scanners, either Signa LX or CVi (GE Medical Systems, Waukesha, WI, USA) or Symphony or Sonata (Siemens Medical Systems, Erlangen, Germany). Long-axis cine images were obtained from 2-chamber and 4-chamber views, using electrocardiogram-gated fast gradient-echo pulse sequences. A stack of short-axis cine images was acquired to encompass both ventricles, and LV end-diastolic volume was measured using cardiac image modeler software (CIM version 6.0, University of Auckland, New Zealand). All the cine images were acquired with a temporal resolution of ~ 50 ms. The complete CMR protocol, as well as details on image analysis, data quality control, calculations for LVEF, LV mass and volumes, LA volumes, and measurement reproducibility, have been published previously (23).

Multimodality tissue tracking software (MTT version 6.0, Toshiba Medical Systems Corporation, Tokyo, Japan) was used to quantify LA volume and strain from 2- and 4-chamber cine CMR images (Supplementary File 2). This method has been validated previously with good to excellent intra- and inter-reader reproducibility with intraclass correlation (ICC) of 0.88 to 0.98 ($p < 0.001$), and good inter-study reproducibility with ICC of 0.44 to 0.82 ($p < 0.05$ to 0.001) (24–26). A single experienced operator, blinded to the participant's case status,

defined endocardial and epicardial borders of the LA at end-systole. Using the marked points, the software creates endocardial and epicardial borders, then tracks LA tissue in subsequent frames. The endocardial and epicardial contours generated by the software are then followed by the operator during the cardiac cycle for quality control.

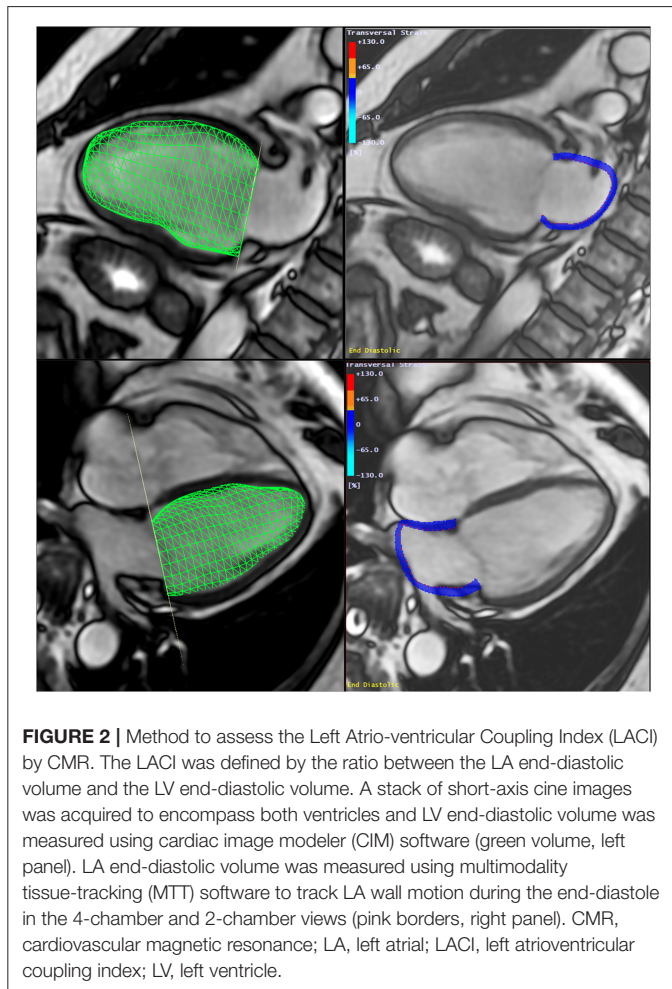
Left Atrioventricular Coupling Index

The LACI was defined by CMR for each participant by the LA end-diastolic volume divided by the LV end-diastolic volume. The LV volume was measured from the stack of short-axis cine images, while the LA volume was measured from the 2-chamber and 4-chamber views, as previously described (Figure 2). The LA and LV volumes were measured in the same end-diastolic phase defined by mitral valve closure.

The LACI value is expressed as a percentage, and a higher LACI indicates greater disproportion between the LA and LV volumes at ventricular end-diastole, reflecting greater impairment of left atrioventricular coupling. Moreover, the Δ LACI is defined by the annual difference in the LACI value measured at baseline, at Exam 1 ($LACI_{Baseline}$) and the LACI value measured after 10-years, at Exam 5 ($LACI_{10-years}$), and the Δ LACI value is expressed as a percentage per year.

Incident Heart Failure

The MESA outcome event ascertainment protocols have been described in detail and are available online (www.mesa-nhlbi.org). In addition to MESA follow-up examinations, a telephone interviewer contacted each participant



(or representative) every 9–12 months to inquire about interim hospital admissions, CV outpatient diagnoses, and mortality.

Medical records were reviewed and diagnoses of HF events, including HF with preserved or reduced ejection fraction, were adjudicated by a panel of MESA physicians using standardized criteria. We used both probable and definite HF events for analysis. Probable HF was defined as a physician diagnosis and a receipt of HF medical treatment with intravenous diuretics. Definite HF required an additional criterion; such as evidence of pulmonary congestion on chest radiography, reduced LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction. Ejection fraction (EF) measures were recorded from clinical echocardiography for events diagnosed as HF by MESA cardiac reviewers. The last HF events data was followed-up to December 2017. To avoid any competitive risk between HF events and AF, we excluded all patients experienced AF during the follow-up.

Statistical Analyses

The baseline and after 10-year participant characteristics are presented as mean \pm standard deviation (SD) for continuous variables and as counts and percentages for categorical variables in **Table 1**. Comparisons employed the χ^2 or Fisher's exact test for

categorical variables and the Student's *t*-test or Mann–Whitney–Wilcoxon test, as appropriate, for continuous variables. We used Cox regression models to study the associations between the LACI, or Δ LACI, and incident HF events. The assumption of proportionality of hazards was confirmed for each model. The cumulative risk of incident HF over the follow-up years for the cohort, stratified by the LACI terciles, or Δ LACI terciles, was determined using Kaplan–Meier curves, censored at the most recent follow-up. Differences across terciles were compared using the log-rank test.

The HF risk prediction model used was the MESA-HF risk model already described (27). Two models were proposed to assess the associations between the Δ LACI, or average annualized change in all other LA and LV parameters, and incident HF. In Model 1, we adjusted for the following traditional MESA-HF risk factors (27) at the second CMR exam after 10-year (Exam 5): age, sex, race, heart rate, body mass index, hypertension, diabetes, smoking status, dyslipidemia, and N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP). Model 2 included the model 1 plus the baseline value of the parameter assessed, measure to account for baseline differences when measuring change, and potential measurement error bias (28).

Model discrimination was assessed with Harrell's C-statistic. Incremental risk prediction was calculated using categorical net reclassification index (NRI) and integrative discrimination index (IDI) for 7-year follow-up. Risk categories for NRI were defined a priori (<5%, 5–10%, and >10%), similar to that used in other studies (27).

The survival tree method was used to determine the cut-off to transform the LACI and Δ LACI into a binary variable with the best predictive value for HF. A two-tailed *p*-value <0.05 was considered statistically significant. All data were analyzed using R software, version 3.6.1 (R Project for Statistical Computing).

RESULTS

Study Population

Among the 4,859 MESA participants with baseline CMR studies including LA volume assessment, 2,250 (46.3%) had at least two CMR exams (baseline and after 10-year follow-up) with LA, LV, and outcome data available (mean age 59.3 ± 9.3 years and 46.7% male participants). Among those, 37.3% had hypertension with 31.2% on antihypertensive therapy, 11.3% were current smokers, 9.6% had diabetes mellitus, and the mean body mass index was 27.8 ± 5.0 kg/m². The baseline characteristics of the study population at Exam 5 after a mean time of 9.6 ± 0.6 years, divided into those who developed HF or not, are presented in **Table 1**. Among the patients excluded due to atrial fibrillation during the follow-up, only 12 patients had incident HF during atrial fibrillation. After a mean follow-up time of 6.8 ± 1.3 years after the second CMR exam, 50 participants had incident HF events. Among these 50 incident HF events, there were 39 definite HF (78%) and 11 probable HF (22%). Of these 50 incident HF events, there were 29 HF with preserved LVEF (58%) and 21 with reduced LVEF (42%).

Participants with HF were older ($p < 0.001$) and had more frequently hypertension ($p < 0.001$) with a higher systolic blood

TABLE 1 | Population characteristics of participants at baseline and at second examination ($n = 2,250$).

Parameters	Baseline (Exam 1) ($n = 2,250$)	Second study (Exam 5), 9.6 ± 0.6 years after baseline		
		No HF ($n = 2,200$)	HF ($n = 50$)	<i>p</i> -Values
Age, years	59.3 ± 9.3	68.6 ± 9.1	76.0 ± 8.9	<0.001
Male, <i>n</i> (%)	1,050 (46.7)	1,026 (46.6)	24 (48.0)	0.962
Ethnicity (Ca/Ch/AA/Hi), %	43/122/24/21	43/12/24/21	25/1/12/12	0.171
Hypertension, <i>n</i> (%)	840 (37.3)	1,226 (55.7)	45 (90.0)	<0.001
Systolic blood pressure, mmHg	123 ± 20	123 ± 20	135 ± 24	0.001
Diastolic blood pressure, mmHg	72 ± 10	68 ± 10	69 ± 11	0.839
Hypertension medication, <i>n</i> (%)	701 (31.2)	1,130 (51.4)	40 (80.0)	<0.001
Body mass index, kg/m ²	27.8 ± 5.0	28.1 ± 5.2	28.7 ± 5.3	0.399
Glycemic status, <i>n</i> (%)				0.021
Normal	1,781 (79.2)	1,381 (62.8)	23 (46.0)	
Impaired fasting glucose	254 (11.3)	443 (20.1)	13 (26.0)	
Diabetes mellitus	215 (9.6)	376 (15.7)	14 (28.0)	
Smoking status, <i>n</i> (%)				
Never	1,178 (52.4)	1,023 (46.5)	14 (28.0)	
Former	817 (36.3)	1,013 (46.0)	33 (66.0)	
Current	255 (11.3)	164 (7.5)	3 (6.0)	
LDL cholesterol, mg/dl	118 ± 31	107 ± 32	91 ± 32	0.001
HDL cholesterol, mg/dl	51 ± 15	56 ± 16	56.4 ± 18	0.877
Lipid-lowering medication, <i>n</i> (%)	331 (14.7)	811 (36.9)	24 (48.0)	0.143
NT-proBNP, pg/ml	73.6 ± 108.2	117.7 ± 122.0	463.4 ± 232.2	<0.001
Framingham CVD risk, %	12.3 ± 8.9	15.2 ± 9.0	20.6 ± 8.5	<0.001
Heart rate, bpm	62 ± 8.9	64.2 ± 10.4	66.8 ± 10.4	0.092
LA parameters				
LAVI _{min} , ml/m ²	11.9 ± 6.2	16.3 ± 8.3	26.1 ± 16.3	<0.001
LAVI _{max} , ml/m ²	30.0 ± 9.4	35.1 ± 11.2	43.9 ± 16.4	<0.001
Peak LA reservoir strain, %	37.0 ± 11.0	31.7 ± 13.7	23.9 ± 16.5	0.002
LV parameters				
LV EDVi, ml/m ²	70.9 ± 12.1	64.4 ± 13.2	67.0 ± 17.3	0.295
LVEF, %	62.6 ± 5.7	62.1 ± 7.1	59.1 ± 9.16	0.027
LV mass index, g/m ²	65.0 ± 11.6	65.7 ± 13.4	76.2 ± 16.3	<0.001
LV MVR, g/ml	0.93 ± 0.17	1.04 ± 0.22	1.20 ± 0.35	0.005
LVGFI, %	40.4 ± 6.1	37.6 ± 6.7	33.0 ± 7.4	<0.001
LACI, %	17.0 ± 8.0	26.1 ± 10.2	41.2 ± 12.1	<0.001

AA, African American; Ca, Caucasian; Ch, Chinese American; Hi, Hispanic; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CVD, cardiovascular disease; HDL, high-density lipoprotein; HF, heart failure; LA, left atrium; LACI, left atrioventricular coupling index; LAVI, left atrium volume indexed; LDL, low-density lipoprotein; EDVi, end-diastolic volume indexed; LV, left ventricle; LVEF, left ventricle ejection fraction; LVGFI, LV global function index; LV/MVR, LV mass/LV volume. Bolded *p*-values correspond to statistically significant results with $p < 0.05$.

pressure level ($p = 0.001$) compared to participants without HF. LA and LV functional parameters were lower (all $p < 0.001$), and LV mass/LV volume higher ($p = 0.005$) in participants with HF compared to those without AF.

LACI and Annualized Change in LACI

For the entire study population, mean baseline LACI was $17.0 \pm 8.0\%$ and at follow up, LACI_{10-years} was $26.3 \pm 10.5\%$, with a mean Δ LACI of $1.3 \pm 1.0\%/year$ (Supplementary File 3). Change in LACI (Δ LACI) and individual LA and LV parameters over 9.6 ± 0.6 years are shown in Supplementary File 4. While participants who developed HF had greater increase in LA volume (Δ LAVI_{min} 1.29 ± 1.28 vs. 0.47 ± 0.81 ml/m²/year, $p < 0.001$) than those who did not, LV end-diastolic volumes decreased similarly with aging in both groups. Of note, correlations between LA and LV end-diastolic volumes were

weak at both baseline and follow up ($R^2 = 0.15$ and $R^2 = 0.10$) (Supplementary File 5).

There was no significant difference in mean LACI between women and men at baseline (LACI_{Baseline} = 16.7 ± 8.2 vs. $16.8 \pm 7.6\%$, $p = 0.66$, respectively), but at follow up, mean LACI was higher in women than in men (LACI_{10-years} = 26.3 ± 12.0 vs. $24.7 \pm 11.2\%$, $p = 0.010$, respectively). Consistently, Δ LACI was higher in women than in men (1.03 ± 1.10 vs. $0.83 \pm 1.00\%/year$, $p < 0.001$, respectively) (Supplementary File 6).

LACI and Incident HF

The results of unadjusted and adjusted Cox proportional hazard models for LACI as well as LA and LV parameters measured after 10-years are presented in Table 2. LACI_{10-years} was positively associated with incident HF before and after adjustment for risk factors (adjusted hazard ratio [HR] 1.44; 95% CI [1.25–1.66] per 1

TABLE 2 | Univariable and multivariable analysis of incident HF according to LACI and other LA or LV parameters after 10 years.

	Univariable analysis		Model 1* HF risk factors	
	Hazard ratio (95% CI)	p-Values	Hazard ratio (95% CI)	p-Values
LACI _{10-years}	1.69 (1.50–1.90)	<0.001	1.44 (1.25–1.66)	<0.001
LACI _{10-years} cut-off >30% [‡]	4.47 (2.57–7.79)	<0.001	2.05 (1.14–3.68)	0.011
LAVI _{min}	1.67 (1.47–1.88)	<0.001	1.40 (1.28–1.68)	<0.001
LAVI _{max}	1.64 (1.36–1.98)	<0.001	1.35 (1.08–1.69)	0.023
Peak LA reservoir strain	0.75 (0.58–0.88)	0.003	0.79 (0.65–0.92)	0.012
LV EDVi	1.20 (0.92–1.57)	0.174	0.95 (0.78–1.16)	0.619
LVEF	0.65 (0.50–0.85)	0.002	0.70 (0.55–0.89)	0.008
LV mass index	1.58 (1.30–1.97)	<0.001	1.44 (1.25–1.66)	<0.001
LACI _{10-years} cut-off >30% [‡]	4.47 (2.57–7.79)	<0.001	2.05 (1.14–3.68)	0.011
LAVI _{min}	1.67 (1.47–1.88)	<0.001	1.40 (1.28–1.68)	<0.001
LAVI _{max}	1.64 (1.36–1.98)	<0.001	1.35 (1.08–1.69)	0.023
Peak LA reservoir strain	0.75 (0.58–0.88)	0.003	0.79 (0.65–0.92)	0.012
LV EDVi	1.20 (0.92–1.57)	0.174	0.95 (0.78–1.16)	0.619
LVEF	0.65 (0.50–0.85)	0.002	0.70 (0.55–0.89)	0.008
LV mass index	1.58 (1.30–1.97)	<0.001	1.22 (1.03–1.52)	0.032
LV MVR	1.64 (1.34–2.02)	<0.001	1.37 (1.07–1.74)	0.016
LVGFI	0.49 (0.37–0.65)	<0.001	0.54 (0.40–0.74)	<0.001
Framingham CVD risk	1.84 (1.39–2.43)	<0.001	1.00 (0.64–1.57)	0.984
tbf<0.001	1.22 (1.03–1.52)	0.032		
LV MVR	1.64 (1.34–2.02)	<0.001	1.37 (1.07–1.74)	0.016
LVGFI	0.49 (0.37–0.65)	<0.001	0.54 (0.40–0.74)	<0.001
Framingham CVD risk	1.84 (1.39–2.43)	<0.001	1.00 (0.64–1.57)	0.984

Of note, each line of this table corresponds to the addition one by one of the LV or LA parameters to the model 1. All LV parameters, LA parameters and LACI values were normalized according to the following formula: (parameter – mean value)/standard deviation. CI, confidence interval; CVD, cardiovascular disease; EDVi, end-diastolic volume indexed; EF, emptying fractions; HF, heart failure; Indexed volumes, maximum (Vlmax), minimum (Vlmin); LA, left atrial; LACI, left atrioventricular coupling index; LAVI, left atrium volume indexed; LV, left ventricle; LVEF, left ventricle ejection fraction; LVGFI, LV global function index; MVR, mass-to-volume ratio.

*Multivariable model 1 (HF risk model) included: age, gender, race, body mass index, hypertension, diabetes, smoking status dyslipidemia, and NT-proBNP.

[‡]LACI_{10-years} used as continuous variable.

[‡]LACI_{10-years} used as binary variable defined by a cut-off >30%. Bolded p-values correspond to statistically significant results with p < 0.05.

SD increment; p < 0.001). LACI_{10-years} top tercile (LACI_{10-years} >28.9%) was more strongly associated with HF incidence than the bottom tercile (<19.7%) (log-rank p < 0.001) (Figure 3A). Using an optimal cut off point to predict incident HF defined by survival tree method (Supplementary File 7), LACI_{10-years} >30% was independently associated with incident HF before (HR 4.47; 95% CI [2.57–7.79], p < 0.001) and after adjustment (adjusted HR 2.05; 95% CI [1.14–3.68], p = 0.011) (Figure 3B).

Annualized Change in LACI and Incident HF

Bivariable and multivariable analyses results for ΔLACI and main LA and LV parameters are presented in Table 3. Annual change in LACI was positively associated with HF after adjustment on LACI_{Baseline} (bivariable analysis), (HR 1.77; 95% CI [1.49–2.09], p < 0.001). After adjusting for traditional MESA-HF risk factors (Model 1) plus LACI_{Baseline} (Model 2), ΔLACI remained independently associated with incident HF (adjusted Model 1 HR 1.56; 95% CI [1.32–1.85] per 1 SD increment;

adjusted Model 2 HR 1.55; 95% CI [1.30–1.85] per 1 SD increment; respectively, p < 0.001 for both). ΔLACI top tercile (>1.3%/year) was more strongly associated with incident HF than the bottom tercile (<0.4%/year) (log-rank p < 0.001) (Figure 4A).

Using an optimal ΔLACI cut-off of >1.5%/year to predict incident HF defined by survival tree method (Supplementary File 8), an increase in ΔLACI of >1.5%/year remained independently associated with greater HF occurrence (adjusted Model 1 HR 2.53; 95% CI [1.44–4.46] per 1 SD increment; adjusted Model 2 HR 2.68; 95% CI [1.51–4.75] per 1 SD increment, respectively, p < 0.001 for both) (Figure 4B).

Atrioventricular Coupling Improvement of HF Risk Prediction

The multivariable model with the LACI_{10-years} showed significant improvement in model discrimination compared to the multivariable model with traditional MESA-HF risk factors for predicting incident HF (C-statistic: 0.81 vs. 0.77;

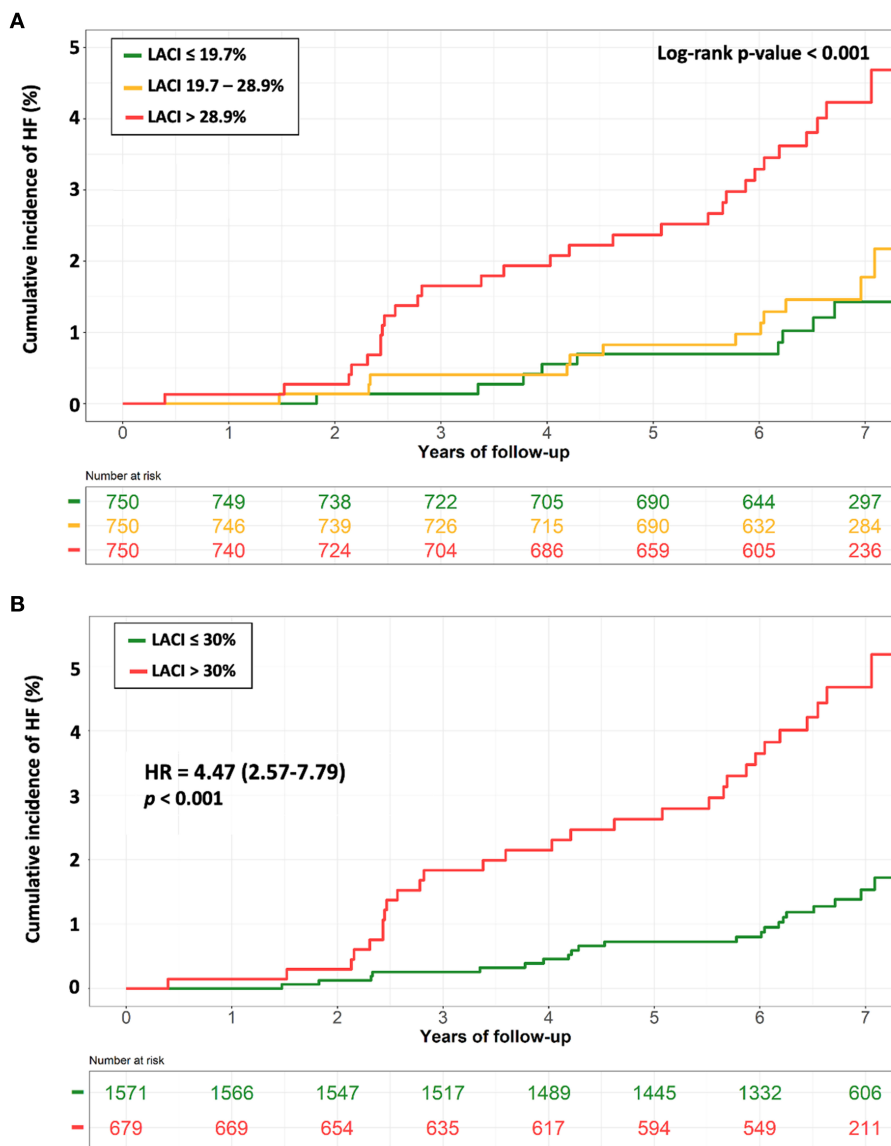


FIGURE 3 | Kaplan-Meier survival curves for incident HF stratified by LACI tertiles **(A)** and by a LACI cut-off of 30% **(B)**. **(A)** The cumulative hazard was significantly greater in the 3rd LACI_{10-years} tertile compared with the other tertiles for incident HF (log-rank for difference; *p* < 0.001). **(B)** The cumulative hazard was significantly greater for patients with LACI_{10-years} >30% compared with patients with LACI_{10-years} ≤30% for incident HF (log-rank for difference; *p* < 0.001). HF, heart failure; LACI, left atrioventricular coupling index.

NRI = 0.411; IDI = 0.043). Follow up exam LACI_{10-years} also demonstrated better discrimination for incident HF than the multivariable model with individual LA or LV parameter plus the traditional MESA-HF risk factors (Table 4).

Improvement in Risk Prediction With Addition of Average Annualized Change in LACI

After adjustment, ΔLACI showed significant improvement in model discrimination compared to the multivariable model with traditional MESA-HF risk factors for predicting incident HF (C-statistic: 0.82 vs. 0.77; NRI = 0.491; IDI = 0.058). ΔLACI also

demonstrated better discrimination for incident HF than the multivariable model with average annualized changes in LA or LV parameters (Table 5).

DISCUSSION

In this multi-ethnic population of participants, aged from 45 to 84 years, and free of clinical CVD at enrollment, our findings suggest the predictive value of both a novel LACI and the average annualized change in LACI, ΔLACI, for predicting incident HF. Indeed, LACI and ΔLACI were independently associated with incident HF, improving model discrimination

TABLE 3 | Bivariable and multivariable analysis of incident HF according to Annual change in LACI and Annual change in other LA or LV parameters.

	Bivariable analysis*		Model 1†		Model 2‡	
	Hazard ratio (95% CI)	p-Values	HF risk factors		Model 1 + Baseline LA/LV variables	
			Hazard ratio (95% CI)	p-Values	Hazard ratio (95% CI)	p-Values
ΔLACI§	1.77 (1.49–2.09)	<0.001	1.56 (1.32–1.85)	<0.001	1.55 (1.30–1.85)	<0.001
ΔLACI cut-off > 1.5%/year	3.74 (2.14–6.55)	<0.001	2.53 (1.44–4.46)	<0.001	2.68 (1.51–4.75)	<0.001
ΔLAVI _{min}	1.69 (1.47–1.93)	<0.001	1.50 (1.25–1.80)	<0.001	1.48 (1.22–1.79)	<0.001
ΔLAVI _{max}	1.52 (1.31–2.02)	<0.001	1.45 (1.11–1.90)	<0.001	1.52 (0.97–1.62)	0.064
ΔPeak LA reservoir strain	0.72 (0.56–0.87)	0.002	0.88 (0.62–1.04)	0.078	0.70 (0.52–0.85)	0.019
ΔLV EDVi	1.17 (0.87–1.58)	0.293	1.15 (0.89–1.47)	0.279	1.14 (0.87–1.46)	0.291
ΔLVEF	0.68 (0.51–0.91)	0.009	0.78 (0.60–1.01)	0.055	0.67 (0.50–0.88)	0.004
ΔLV mass index	1.59 (1.39–2.10)	<0.001	1.27 (0.99–1.61)	0.065	1.51 (1.26–1.82)	<0.001
ΔLV MVR	1.48 (1.19–1.85)	<0.001	1.24 (0.98–1.57)	0.071	1.32 (1.04–1.67)	0.020
ΔLVGFI	0.51 (0.37–0.70)	<0.001	0.77 (0.59–1.00)	0.051	0.75 (0.56–1.05)	0.065
ΔFramingham CVD risk	1.20 (0.89–1.60)	0.228	1.01 (0.79–1.29)	0.920	1.02 (0.74–1.40)	0.912

Of note, each line of this table corresponds to the addition one by one of the changes in LV or LA parameters to the models 1 or 2. All variables values were expressed per 1-SD/year and normalized according to the following formula: (Variable measured – mean value)/standard deviation. Δ, Annual change; CI, confidence interval; CVD, cardiovascular disease; EDVi, end-diastolic volume indexed; EF, emptying fractions; HF, heart failure; Indexed volumes, maximum (V_{max}), minimum (V_{min}); LA, left atrial; LACI, left atrioventricular coupling index; LV, left ventricle; LVEF, left ventricle ejection fraction; LVGFI, LV global function index; MVR, mass-to-volume ratio.

*Bivariable model included both the annual change in the variable and the value of the variable measured at baseline.

† Multivariable **model 1** (HF risk model) included: age, gender, race, body mass index, hypertension, diabetes, smoking status dyslipidemia and NT-proBNP.

‡ Multivariable **model 2** included: model 1 + baseline value measured at Exam 1 for each LA or LV parameters.

§ ΔLACI used as continuous variable.

|| ΔLACI used as binary variable defined by a cut-off > 1.5%/year. Bolded p-values correspond to statistically significant results with p < 0.05.

and reclassification beyond traditional MESA-HF risk factors. To our knowledge, the prognostic value of this index and its incremental prognostic value over and above traditional MESA-HF risk factors have not been previously reported.

In our study, LACI and ΔLACI were stronger independent predictors of incident HF than the Framingham score and individual LA or LV parameters, resulting in improved discrimination and reclassification for incident HF. The increase in LA volume relative to that of the LV at end-diastole reflects impaired LV compliance, leading to a reduction of LA reservoir function, which have been described as significant predictors of incident HF (9). Using the survival tree method, we also investigated the best LACI and ΔLACI cut-off points to predict incident HF, and found that LACI >30% and ΔLACI >1.5%/years were also independently associated with incident HF. Therefore, LACI appears to reflect an earlier stage of LA remodeling than individual LA parameters, having stronger prognostic value for predicting incident HF before and after adjustment for traditional MESA-HF risk factors. In line with previous reports (9), these findings suggest that HF may not occur exclusively because of impaired LV structure or function, but may also be susceptible to uncoupling of LA and LV structure and function as markers of early LV diastolic dysfunction. Interestingly, although the multivariable model with the peak LA reservoir strain showed significant improvement in model discrimination and reclassification compared to the multivariable model with traditional MESA-HF risk factors for predicting incident HF, this study did not show an incremental prognostic

value of the annual change in peak LA reservoir strain to predict incident HF.

A previous CMR study performed in 40 healthy individuals has described that the oldest individuals had larger LA and smaller LV volumes with larger LA/LV end-diastolic volume ratio (27 ± 6 vs. 19 ± 3%; p < 0.001) and preserved LVEF (29). These effects of aging on left atrioventricular coupling and LV filling are consistent with our findings. Consistently, in a canine model of early-stage hypertensive HF with preserved LVEF, left atrioventricular coupling assessed by CMR was impaired and the curvilinear LA end-reservoir pressure-volume relationship was shifted upward and leftward, indicating reduced LA compliance (30). Consistently, a recent study described a LACI measured by echocardiography as a prognosticator of death in patients with HF with reduced LVEF or degenerative mitral disease and regurgitation (31). Thus, all these findings emphasize the prognostic importance of atrioventricular coupling reflected by intricate hemodynamic interactions between LA and LV during LV diastole (32).

Regarding the question of the optimal time of the cardiac cycle to assess this LACI, some reports have described the important interaction between the performance of LA and LV, in the absence of mitral valve disease, particularly at the end of LV diastole (15, 16). Furthermore, a recent study has consistently suggested that both LA end-diastolic volume (33, 34) and LA end-diastolic volume change (35, 36) are more closely correlated with LV filling pressure and the occurrence of CV events, including HF, than these same measurements measured in systole (16).

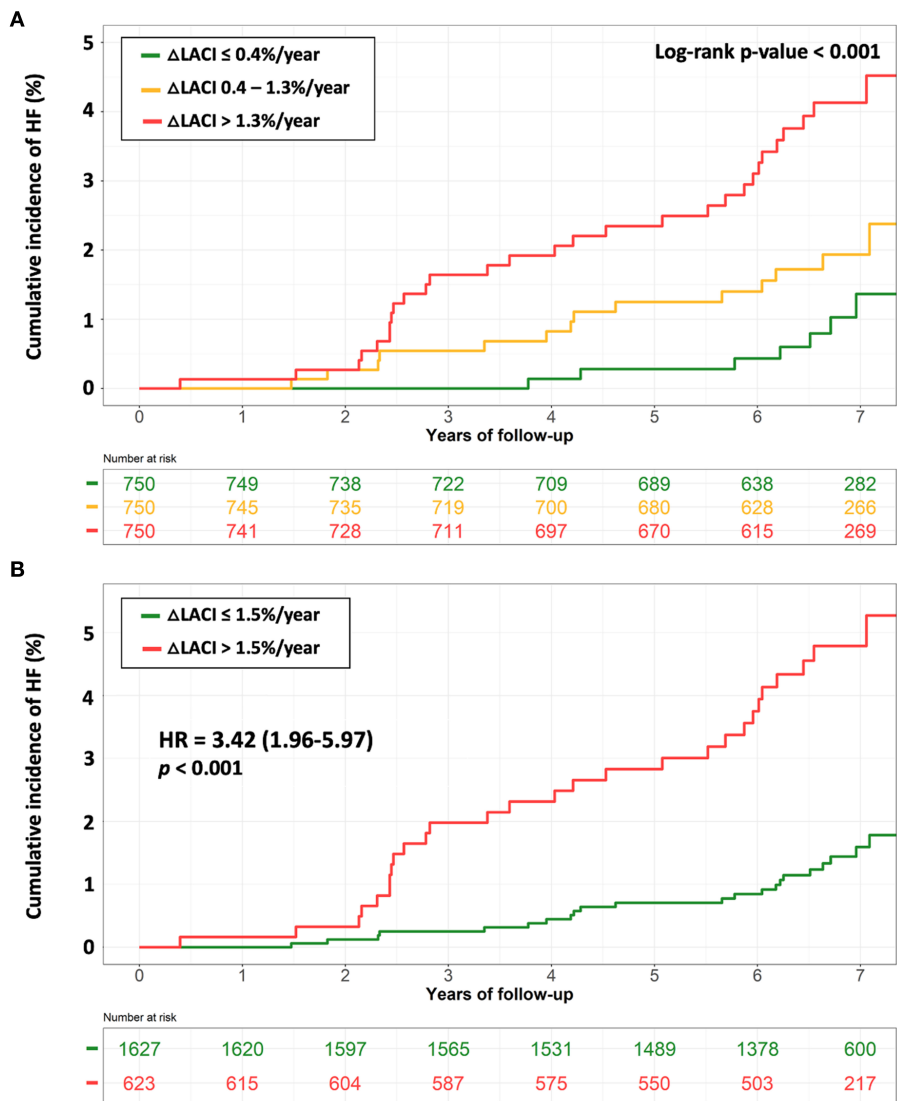


FIGURE 4 | Kaplan-Meier survival curves for incident HF stratified by tertiles of ΔLACI (A) and by ΔLACI with a cut-off of 1.5%/year (B). (A) The cumulative hazard was significantly greater in the 3rd tertile compared with the other tertiles for incident HF (log-rank for difference; $p < 0.001$). (B) The cumulative hazard was significantly greater for patients with $\Delta\text{LACI} > 1.5\%/year$ compared with patients with $\Delta\text{LACI} \leq 1.5\%/year$ for incident HF (log-rank for difference; $p < 0.001$). Δ , annual change; HF, heart failure; LACI, left atrioventricular coupling index.

To investigate the important interaction between LA and LV performance during the LV end-diastole some studies have evaluated in detail the ventricular filling mechanism. During the LV diastole, the passive filling creates an early blood flow vortex inside the LV at the beginning of LV diastole (17). This diastolic blood flow vortex generates an important kinetic energy and redirects the incoming LA inflow toward the LV outflow tract, priming the LV by stretching cardiomyocytes and maximizing pre-load before the onset of LV systolic contraction (37). All of these mechanisms emphasize the important hemodynamic diastolic interactions between LA and LV, possibly in part explaining the prognostic value of left atrioventricular coupling measured at that moment (LACI).

Finally, early detection of a subclinical left atrioventricular coupling impairment could pave the way to new therapeutic strategies that might slow or change their clinical history, impacting on their quality of life and mortality. Further studies could be proposed, evaluating early pharmacologic effects on left atrioventricular coupling.

Study Limitations

In this study, LACI was investigated as a diagnostic tool for early detection of HF risk in asymptomatic participants without known CVD. Because LACI may not be regarded as an ideal assessment tool for individuals with pronounced LA and LV enlargement in case of advanced structural heart disease, the

TABLE 4 | Discrimination and reclassification associated with LACI to different LA and LV parameters at 10-years of follow-up to predict incident HF.

	Incident HF		
	C-index (95%CI)	NRI (95%CI)	IDI (95%CI)
Model 1* (HF risk factors)	0.77 (0.73–0.82)	Reference	Reference
Model 1 + LACI _{10-years} [†]	0.81 (0.74–0.87)	0.411 (0.042–0.780)	0.043 (0.016–0.106)
Model 1 + LACI _{10-years} cut-off >30% [‡]	0.80 (0.73–0.86)	0.607 (0.063–0.843)	0.039 (0.011–0.107)
Model 1 + LAVI _{min}	0.80 (0.73–0.86)	0.201 (-0.219–0.486)	0.038 (0.010–0.104)
Model 1 + LAVI _{max}	0.78 (0.74–0.82)	0.328 (0.050–0.573)	0.015 (0.004–0.041)
Model 1 + Peak LA reservoir strain	0.79 (0.73–0.85)	0.312 (0.047–0.599)	0.017 (0.006–0.044)
Model 1 + LV EDVi	0.77 (0.73–0.82)	0.075 (-0.222–0.372)	0.000 (-0.001–0.010)
Model 1 + LVEF	0.80 (0.74–0.86)	0.369 (0.158–0.580)	0.039 (0.010–0.109)
Model 1 + LV mass index	0.79 (0.72–0.85)	0.248 (0.137–0.398)	0.018 (0.009–0.067)
Model 1 + LV MVR	0.79 (0.73–0.85)	0.259 (0.143–0.402)	0.020 (0.012–0.069)
Model 1 + LVGFI	0.80 (0.74–0.85)	0.382 (0.157–0.607)	0.031 (0.015–0.085)
Model 1 + Framingham CVD risk	0.77 (0.73–0.82)	0.065 (-0.192–0.337)	0.001 (-0.001–0.012)

All LV parameter, LA parameter and LACI values were normalized according to the following formula: (parameter–mean value)/standard deviation. For each model, discrimination and reclassification were based on net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Results are for 7-year follow-up. CI, confidence interval; CVD, cardiovascular disease; EDVi, end-diastolic volume indexed; EF, emptying fractions; HF, heart failure; Indexed volumes, maximum (V_{max}), minimum (V_{min}); LA, left atrial; LACI, left atrioventricular coupling index; LV, left ventricle; LVEF, left ventricle ejection fraction; MVR, mass-to-volume ratio.

*Multivariable **model 1** (HF risk model) included: age, gender, race, body mass index, hypertension, diabetes, smoking status, dyslipidemia, and NT-proBNP.

[†]LACI_{10-years} used as continuous variable.

[‡]LACI_{10-years} used as binary variable defined by a cut-off > 30%.

TABLE 5 | Discrimination and reclassification associated with Annual change in LACI to change in different LA and LV parameters to predict incident HF.

	Incident HF		
	C-index (95%CI)	NRI (95%CI)	IDI (95%CI)
Model 1* (HF risk factors)	0.77 (0.73–0.82)	Reference	Reference
Model 2 [†] + ΔLACI [‡]	0.82 (0.76–0.89)	0.491 (0.048–0.934)	0.058 (0.028–0.096)
Model 2 [†] + ΔLACI cut-off>1.5%/year [§]	0.81 (0.75–0.87)	0.536 (0.050–0.998)	0.045 (0.024–0.083)
Model 2 [†] + ΔLAVI _{min}	0.80 (0.75–0.85)	0.455 (0.003–0.907)	0.031 (0.008–0.076)
Model 2 [†] + ΔLAVI _{max}	0.79 (0.74–0.83)	0.270 (-0.010–0.482)	0.019 (0.002–0.072)
Model 2 [†] + ΔPeak LA reservoir strain	0.77 (0.73–0.82)	0.009 (-0.178–0.281)	0 (-0.002–0.007)
Model 2 [†] + ΔLV EDVi	0.77 (0.73–0.82)	-0.013 (-0.172–0.198)	0 (-0.002–0.009)
Model 2 [†] + ΔLVEF	0.77 (0.73–0.82)	0.010 (-0.182–0.278)	0 (-0.001–0.008)
Model 2 [†] + ΔLV mass index	0.80 (0.75–0.84)	0.428 (0.002–0.876)	0.030 (0.007–0.075)
Model 2 [†] + ΔLV MVR	0.79 (0.73–0.85)	0.251 (-0.030–0.532)	0.016 (0.002–0.053)
Model 2 [†] + ΔLVGFI	0.80 (0.74–0.86)	0.466 (0.006–0.926)	0.033 (0.011–0.080)
Model 2 [†] + Δ Framingham CVD risk	0.77 (0.73–0.82)	-0.052 (-0.246–0.262)	0 (-0.001–0.008)

All variables values were expressed per 1-SD/year and normalized according to the following formula: (Variable measured – mean value)/standard deviation. For each model, discrimination and reclassification were based on net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Results are for 7-year follow-up. Δ, Annual change; CI, confidence interval; CVD, cardiovascular disease; EDVi, end-diastolic volume indexed; EF, emptying fractions; Indexed volumes, maximum (V_{max}), minimum (V_{min}); LA, left atrial; LACI, left atrioventricular coupling index; LV, left ventricle; LVEF, left ventricle ejection fraction; MVR, mass-to-volume ratio.

*Multivariable **model 1** (HF risk model) included: age, gender, race, body mass index, hypertension, diabetes, smoking status, dyslipidemia and NT-proBNP.

[†]Multivariable **model 2** included: model 1 + baseline value measured at Exam 1 for each LA or LV parameters.

[‡]ΔLACI used as continuous variable.

[§]ΔLACI used as binary variable defined by a cut-off>1.5%/year.

extension of our findings to populations with established CVD require additional evaluation. Due to the relatively low incidence of HF, the current findings should be analyzed with precaution. However, the exclusion of all participants with significant valvular disease, myocardial infarction, or atrial fibrillation at the

starting time of the time-dependent analysis reduces the risk of confounding bias. In addition, HF was not differentiated into HF with preserved or reduced LVEF, due to the limited power for sub-analysis given the low number of events. Moreover, the main cause of HF was not adjudicated in all patients.

This study allowed to assess the incremental value of LACI and Δ LACI beyond traditional MESA-HF risk factors but not beyond LV parameters such as LVEF because due to a risk of collinearity in the model. Because the distribution of LACI and Δ LACI were not exactly normal, the time-dependent analyses used scaled LACI (LACI-mean value/SD) and scaled Δ LACI (Δ LACI-mean value/SD), which makes its clinical interpretation less easy. Δ LACI was averaged across ten years, thus assuming linearity over time. This method may not have fully captured the variation in year-to-year measurements thus providing additional precedence for further investigation. In this regard, the concept of dynamic change in risk profile, as participants age and accumulate exposure to risk factors, has been explored using other prediction models in cardiology, suggesting that risk profile change may be superior to single baseline assessments (38–40). We also used two instead of three dimensional methods to measure LA volumes, which may have underestimated true volumes by 11.5–20% (41). However, this method has been widely used and validated in clinical studies, being particularly suitable for population work with large sample sizes such as the present study (24, 25). Dedicated LV fibrosis parameters such as T1 mapping or late gadolinium enhancement were not available to perform specific analysis. Although the current study provides important clues to understand the HF pathophysiology and the potential role of the left atrioventricular coupling, the relatively low event rate warrants further studies to validate the prognostic value of LACI and its annual change.

CONCLUSION

In a large multi-ethnic population free of clinical CVD at baseline, impaired left atrioventricular coupling reflected as greater LACI and Δ LACI measured by CMR, were associated with higher risk of incident HF during a 7-year median follow-up. The addition of LACI and Δ LACI to risk prediction models for incident HF improved model discrimination and reclassification for incident HF risk. Future studies should validate these findings to better understand the role of left atrioventricular coupling in HF pathophysiology and risk prediction.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Standard Operating Procedures (SOPs) of the IRBs. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors participated in the discussion of the concept of the study. TP, BA, and JL analyzed data and drafted the manuscript with critical revision. As authors, we attest to each of our substantial contributions to the manuscript and revision. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2021.704611/full#supplementary-material>

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Partie 7 :

Étude n°6 : Intelligence artificielle pour l'automatisation de la mesure du LACI par IRM cardiaque

AI-Based Fully Automated Left Atrioventricular Coupling Index as a Prognostic Marker in Patients Undergoing Stress CMR

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Les cinq premières études de ce travail de thèse ont permis de décrire le premier index de couplage auriculo-ventriculaire gauche, le LACI, et de démontrer la forte valeur pronostique du LACI et de sa variation annualisée moyenne pour prédire de plusieurs évènements cardiovasculaires, incluant l'insuffisance cardiaque et la fibrillation atriale. Cependant, la diffusion de l'utilisation de ce nouvel outil de stratification pronostique est limitée par le fait que cette mesure n'était pas automatisée. Ainsi, l'objectif de cette nouvelle étude était d'évaluer la faisabilité et la bonne performance de la mesure du LACI de façon complètement automatique par un logiciel basé sur l'intelligence artificielle. De plus, cette étude réalisée sur une cohorte française de patients adressés pour une IRM cardiaque de stress pharmacologique permet d'investiguer pour la première fois la valeur pronostique du LACI dans une population avec une maladie cardiovasculaire existante au moment de sa mesure.

Ainsi, l'objectif de cette étude n°6 visait à déterminer chez les patients adressés pour une IRM cardiaque de stress si la mesure du LACI entièrement automatisée par intelligence artificielle pouvait fournir une valeur pronostique additionnelle pour prédire le risque de survenue d'insuffisance cardiaque. Entre 2016 et 2018, les auteurs ont mené une étude longitudinale incluant tous les patients consécutifs adressés pour une IRM cardiaque de stress. Le LACI a été défini comme le rapport des volumes télédiastoliques de l'oreillette gauche et du ventricule gauche. Le critère de jugement principal comprenait l'hospitalisation pour insuffisance cardiaque aiguë ou le décès cardiovasculaire. La régression de Cox a été utilisée pour évaluer l'association du LACI avec le critère de jugement principal après ajustement sur les facteurs de risque traditionnels.

Chez 2134 patients (65 ans, 77 % d'hommes), le LACI était positivement associé au critère de jugement principal après un suivi médian de 5,2 ans avant et après ajustement sur les facteurs de risque dans la population globale (HR 1,18 ; IC à 95 % [1,13-1,24]), chez les patients présentant un IRM cardiaque de stress anormale avec ischémie et/ou réhaussement tardif (HR 1,22 ; IC à 95 % [1,14-1,30]) et chez les patients présentant une IRM cardiaque normale (HR 1,12 ; IC à 95 % [1,05-1,20]) (tous $p < 0,001$). Après ajustement, une valeur de LACI supérieure à 25 % a montré la plus grande amélioration de discrimination et de reclassification du modèle final par rapport aux facteurs de risque traditionnels et aux résultats classiques de l'IRM cardiaque de stress (amélioration du C-index : 0,16 ; amélioration du NRI = 0,388 ; amélioration de l'IDI = 0,153, tous $p < 0,001$).

En résumé, les principaux résultats de l'étude n°6 étaient :

- Dans la population globale, 11,5 % ont atteint le résultat principal, y compris l'hospitalisation pour insuffisance cardiaque aiguë ou un décès cardiovasculaire après un suivi médian de 5,2 ans ;

- La mesure LACI entièrement automatisée basée sur l'IA était réalisable chez 98,0 % des patients référés pour une IRM cardiaque de stress avec une bonne précision ;
- Le LACI était indépendamment associé au critère de jugement principal (insuffisance cardiaque ou mortalité de cause cardiovasculaire) chez les patients présentant une IRM cardiaque de stress anormale et normale ;
- Le LACI a amélioré la discrimination et la reclassification au-delà des facteurs de risque traditionnels et des résultats d'IRM cardiaque de stress, y compris la présence d'ischémie inductible ou de rehaussement tardif ischémique pour la prédiction du critère de jugement principal.

ORIGINAL RESEARCH

AI-Based Fully Automated Left Atrioventricular Coupling Index as a Prognostic Marker in Patients Undergoing Stress CMR

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ABSTRACT

BACKGROUND The left atrioventricular coupling index (LACI) is a strong and independent predictor of heart failure (HF) in individuals without clinical cardiovascular disease. Its prognostic value is not established in patients with cardiovascular disease.

OBJECTIVES The study sought to determine in patients undergoing stress cardiac magnetic resonance (CMR) whether fully automated artificial intelligence-based LACI can provide incremental prognostic value to predict HF.

METHODS Between 2016 and 2018, the authors conducted a longitudinal study including all consecutive patients with abnormal (inducible ischemia or late gadolinium enhancement) vasodilator stress CMR. Control subjects with normal stress CMR were selected using propensity score matching. LACI was defined as the ratio of left atrial to left ventricular end-diastolic volumes. The primary outcome included hospitalization for acute HF or cardiovascular death. Cox regression was used to evaluate the association of LACI with the primary outcome after adjustment for traditional risk factors.

RESULTS In 2,134 patients (65 ± 12 years, 77% men, 1:1 matched patients [1,067 with normal and 1,067 with abnormal CMR]), LACI was positively associated with the primary outcome (median follow-up: 5.2 [IQR: 4.8-5.5] years) before and after adjustment for risk factors in the overall propensity-matched population (adjusted HR: 1.18 [95% CI: 1.13-1.24]), in patients with abnormal CMR (adjusted HR per 0.1% increment: 1.22 [95% CI: 1.14-1.30]), and in patients with normal CMR (adjusted HR per 0.1% increment: 1.12 [95% CI: 1.05-1.20]) (all $P < 0.001$). After adjustment, a higher LACI of ≥25% showed the greatest improvement in model discrimination and reclassification over and above traditional risk factors and stress CMR findings (C-index improvement: 0.16; net reclassification improvement = 0.388; integrative discrimination index = 0.153, all $P < 0.001$; likelihood ratio test $P < 0.001$).

CONCLUSIONS LACI is independently associated with hospitalization for HF and cardiovascular death in patients undergoing stress CMR, with an incremental prognostic value over traditional risk factors including inducible ischemia and late gadolinium enhancement. (J Am Coll Cardiol Img 2023;■:■-■) © 2023 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS**

AI	= artificial intelligence
CAD	= coronary artery disease
CMR	= cardiac magnetic resonance
HF	= heart failure
IDI	= integrative discrimination index
LA	= left atrial
LACI	= left atrioventricular coupling index
LGE	= late gadolinium enhancement
LR	= likelihood ratio
LV	= left ventricular
LVEF	= left ventricular ejection fraction
MI	= myocardial infarction
NRI	= net reclassification improvement

Hear failure (HF) is a leading cause of death worldwide and a major public health problem.¹ Given the important medico-economic burden associated with HF, early detection of these high-risk individuals is crucial. Coronary artery disease (CAD) accounts for more than two-thirds of HF cases.² Studies have emphasized the prognostic role of stress cardiac magnetic resonance (CMR) to predict the occurrence of acute HF and cardiovascular death.³⁻⁵ Indeed, stress CMR has emerged as an accurate and cost-effective modality for risk stratification of cardiovascular events without ionizing radiation.⁶⁻⁸ Numerous studies have shown the incremental prognostic value of inducible ischemia and late gadolinium enhancement (LGE) to predict cardiovascular events and incident HF.^{3,4,6,8}

In addition to the assessment of conventional left ventricular (LV) functional and structural parameters,⁹ recent studies have emphasized the prognostic relevance of left atrioventricular coupling beyond the influences of left atrial (LA) and LV parameters measured separately.^{10,11} From the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, the novel left atrioventricular coupling index (LACI) (ratio of the LA to the LV end-diastolic volumes by CMR)¹⁰ had incremental prognostic value for predicting incident HF, incident atrial fibrillation, and cardiovascular death, above traditional risk factors.^{10,12,13} However, the prognostic value of LACI has only been assessed in the MESA community study among individuals without history of prior cardiovascular disease using CMR.

By contrast, the present study aims to determine whether artificial intelligence (AI)-based fully automated LACI can provide incremental prognostic value above traditional cardiovascular risk factors for predicting HF events among patients undergoing vasodilator stress CMR.

METHODS

STUDY POPULATION. Between January 2016 and December 2018, we conducted a single-center longitudinal study with retrospective enrolment of all consecutive patients with abnormal stress CMR in our laboratory accredited by the European Association of

Cardiovascular Imaging. As previously described,^{6,8,14} abnormal CMR was defined by the presence of inducible ischemia or LGE. A cohort of control subjects with normal stress CMR was selected using a propensity matching score detailed subsequently. Main exclusion criteria were contraindication to CMR or dipyridamole, allergy to gadolinium, glomerular filtration rate <30 mL/min/1.73 m², and known cardiomyopathy (eg, hypertrophic, dilated, arrhythmogenic right ventricular, or infiltrative) and acute or chronic myocarditis ([Supplemental Methods 1](#)). Patients with a magnetic resonance-conditional pacemaker were included. Clinical data were collected according to medical history and clinical examination on the day of stress CMR. All patients provided informed written consent. The study was approved by the local Ethic Committee of our institutions and conducted in accordance with the 1964 Declaration of Helsinki. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for cohort studies.

PATIENT FOLLOW-UP AND CLINICAL OUTCOMES.

The follow-up consisted of a clinical visit as part of usual care (33.0%) or by direct contact with the subject or the referring cardiologist (67.0%). A clinical questionnaire with a detailed description of clinical study outcomes was filled out by senior cardiologists. Data collection ended in January 2022. The primary outcome was a composite outcome including hospitalization for acute HF or cardiovascular death. Hospitalization for acute HF was defined by the use of intravenous diuretic agents combined with a previous history of hospitalization with symptoms and/or signs of HF with evidence of diastolic or systolic dysfunction by echocardiography and elevated levels of natriuretic peptide (B-type natriuretic peptide >35 pg/mL and/or N-terminal pro-B-type natriuretic peptide >125 pg/mL), according to guidelines.² Cardiovascular death was defined as sudden cardiac death with documented fatal arrhythmias, or any death immediately preceded by acute myocardial infarction (MI), acute or exacerbation of HF, or stroke. In patients with multiple events, only the first event was considered for event-free survival analysis. Secondary outcomes included incident HF, cardiovascular death, all-cause death, nonfatal MI, late coronary revascularization, and ventricular tachycardia. All clinical

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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events were defined according to the published standardized definitions¹⁵ and are detailed in [Supplemental Methods 2](#). Clinical event adjudication was based on the follow-up clinical visit or contact, with a consensus reached by 2 senior cardiologists. In patients who underwent percutaneous coronary intervention <90 days after the index CMR examination, periprocedural events (MI or cardiovascular death) were not included in the analysis.

CMR PROTOCOL. The detailed CMR protocol has been previously described,¹⁶ and is detailed in the [Supplemental Methods 3](#). Briefly, CMR was performed in a dedicated CMR laboratory on 1.5-T scanners (MAGNETOM Aera; Siemens Healthineers). Long-axis and short-axis views covering the entire LV were obtained using balanced steady-state free-precession sequence. Vasodilatation was induced with dipyridamole injected at 0.84 mg/kg over 3 minutes for all patients. At the end of vasodilator agent infusion, a bolus of gadolinium-based contrast agent (0.1 mmol/kg; Dotarem) was injected at a rate of 5.0 mL/s. Stress perfusion imaging was performed using a saturation-prepared balanced steady-state free-precession sequence. As already published,^{3,17} to verify the good response to the vasodilator stress agent, we measured the rate-pressure product ([pressure (mm Hg) × heart rate (beats/min)]/1,000 at baseline and at stress). A series of 6 slices (4 short-axis views, in addition to 2- and 4-chamber views) were acquired every other heartbeat. Ten minutes after contrast injection, a single-breath-hold 3-dimensional T1-weighted inversion recovery gradient-echo sequence was acquired with the same prescriptions to detect LGE. The inversion time was individually adjusted to null normal myocardium. CMR sequence parameters are detailed in [Supplemental Table 1](#). Patients were asked to refrain from caffeine at least 12 hours before CMR. Safety was studied with clinical monitoring 1 hour after CMR to assess major adverse events. A 12-lead electrocardiogram was performed both before and after CMR examination.

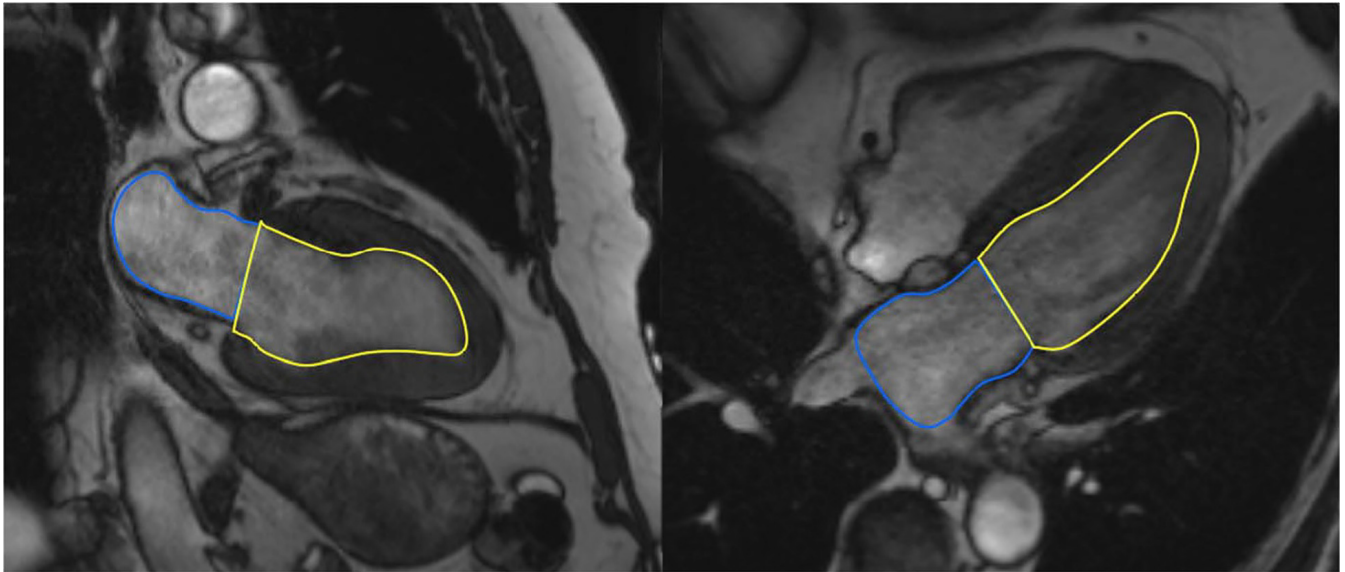
CMR ANALYSIS. LV volumes and left ventricular ejection fraction (LVEF) were calculated from the short-axis cine images (syngo.via; Siemens Healthineers). Stress perfusion and LGE images were evaluated according to the 17-segment model of the American Heart Association.¹⁸ The analysis of perfusion images was done visually by 2 experienced physicians (T.P. and F.S.) blinded to clinical and follow-up data. In the case of a disagreement between these 2 physicians, a third expert physician (J.G.) would make the conclusion. Inducible ischemia was

defined as a subendocardial perfusion defect that: 1) occurred in at least 1 myocardial segment; 2) persisted for at least 3 phases beyond peak contrast enhancement; 3) followed a coronary distribution; and 4) occurred in the absence of colocalized LGE in the same segment.^{3,6,8} MI was defined by LGE with ischemic patterns defined by subendocardial or transmural LGE.¹⁹ The total number of ischemic segments was calculated for each patient. LGE with ischemic patterns was semi-quantitatively assessed using the number of LGE segments. All clinical and CMR characteristics were reported in a dedicated database (Hemolia, Clinigrad Inc).

LEFT ATRIOVENTRICULAR COUPLING INDEX. As recently described,¹⁰ the LACI was defined as the ratio of the LA end-diastolic volume to the LV end-diastolic volume using CMR ([Figure 1](#)). A fully automatic machine learning algorithm was trained and validated on unseen CMR studies to assess the LACI from long-axis cine images (2- and 4-chamber views). The AI algorithm combines multiple deep learning networks for detection and segmentation with an active contours approach to segment the LV and LA in individual 2-dimensional long-axis views images.²⁰ The deep learning networks were trained on more than 1,000 CMR studies from heterogeneous sources.^{21,22} The AI segmentation algorithm was additionally validated on publicly available data.²² On random subsets of 60 patients for the LV and 378 patients for the LA, the average dice score was 89.4 ± 5.7 for the LV and 87.9 ± 12.7 for the LA. The LV and the LA volumes were measured from the 2- and 4-chamber views based on the automatic AI segmentation result using the biplane Simpson method, as previously described.¹⁰ The LA and LV volumes were measured in the same end-diastolic phase defined by the largest LV volume.

In line with prior reports,^{10,12,13} the LACI value was expressed as a percentage, and a higher LACI indicates a greater disproportion between LA and LV volumes during LV end-diastole, reflecting greater impairment of left atrioventricular coupling. As described in MESA, the LACI was transformed into a binary variable using the cutoff of 25%.¹⁰ This cutoff was consistent with the best LACI cutoff of 26.2% able to predict the primary outcome using the survival tree method on the overall propensity-matched population ([Supplemental Figure 1](#)).

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD, categorical variables as frequency and percentage, and follow-up as median and IQR. Comparison of patient characteristics used the Mann-Whitney test for continuous variables and the Pearson's chi-square test for categorical variables.

FIGURE 1 AI-Based Fully Automated LACI

Example of the left atrial (blue line) and left ventricular (yellow line) AI-based fully automated segmentation in a 65-year-old male patient with hypertension and diabetes, presenting atypical angina to assess the LACI by CMR defined by the ratio between the LA end-diastolic volume and the LV end-diastolic volume from long-axis cine images (2- and 4-chamber views). AI, artificial intelligence; CMR, cardiac magnetic resonance; LA, left atrial; LACI, left atrioventricular coupling index; LV, left ventricular.

The dice score was used to measure the accuracy of the automatic segmentation of the LA and LV from long-axis views images. Survival probabilities of the primary outcome were estimated using the Kaplan-Meier method and the survival curves compared with the log-rank test. Data of patients who were lost to follow-up were censored at the time of the last contact. Cox proportional hazards methods were used to identify the predictors of the primary outcome. The proportional hazards assumption was visually assessed using Schoenfeld residuals. Martingale residuals were used to detect nonlinearity in continuous variables.

To assess the incremental prognostic value of LACI, different multivariable models were used for adjustment: 1) model 1 (traditional HF risk factors) involved adjustment for traditional risk factors at baseline including age, male sex, body mass index, diabetes, hypertension, smoking, dyslipidemia, known CAD, and history of HF; 2) model 2 (stress CMR model) involved model 1 + LVEF, presence of inducible ischemia, or LGE with ischemic pattern; and 3) model 3 (LACI model) involved model 2 + LACI value. The discriminative capacity of each model for predicting the primary outcome was determined according to Harrell's C-index before and after addition of LACI. The additional predictive value of the LACI value was calculated by Harrell's C-index increment, integrative

discrimination index (IDI), continuous net reclassification improvement (NRI), and likelihood ratio (LR) test.

To assess potential differences in the prognostic relevance of LACI in patients with abnormal and normal stress CMR, a cohort of control subjects with normal CMR stress was selected using a strictly 1:1 propensity score-matched population. A non-parsimonious multivariable logistic regression model was built to estimate a propensity score for abnormal CMR,²³ using abnormal CMR as the dependent variable and the characteristics listed in [Table 1](#). Imbalances between groups were considered using absolute standardized mean differences <0.2 calculated using Yang and Dalton's method and used as a proxy of covariate balance ([Supplemental Figure 2](#)).²⁴ The probit model with 1-to-1 nearest-neighbor matching and without replacement was used to identify 1 subject with normal CMR (n = 1,067) for each subject with abnormal CMR (n = 1,067).

Forest plots were obtained, and interactions between the tested variables and the effects of LACI on the occurrence of the primary outcome were determined using a partial likelihood ratio test. A 2-tailed value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using R software version 3.6.0 (R Project for Statistical Computing).

TABLE 1 Baseline Characteristics of the Propensity-Matched Population (Normal vs Abnormal CMR)

	Overall Propensity-Matched Population (N = 2,134)	After Propensity Matching 1:1		P Value
		Normal CMR (n = 1,067)	Abnormal CMR (n = 1,067)	
Demographics				
Age, y	65 ± 12	65 ± 12	65 ± 11	0.546
Male	1,637 (76.7)	816 (76.5)	821 (76.9)	0.798
BMI, kg/m ²	27.5 ± 5.1	27.4 ± 5.1	27.5 ± 5.2	0.565
Cardiovascular risk factors				
Diabetes mellitus	625 (29.3)	304 (28.5)	321 (30.1)	0.419
Hypertension	1,108 (51.9)	551 (51.6)	557 (52.2)	0.795
Dyslipidemia	1,117 (52.3)	559 (52.4)	558 (52.3)	0.965
Current or previous smoking	635 (29.8)	314 (29.4)	321 (30.1)	0.740
Family history of CAD	220 (10.3)	114 (10.7)	106 (9.9)	0.569
Obesity (BMI ≥30 kg/m ²)	533 (25.0)	259 (24.3)	274 (25.7)	0.453
Medical history of CV disease				
Known CAD	887 (41.6)	434 (40.7)	453 (42.5)	0.404
PCI	579 (27.1)	286 (26.8)	293 (27.5)	0.733
CABG	125 (5.9)	57 (5.3)	68 (6.4)	0.311
Known MI	572 (26.8)	281 (26.3)	291 (27.3)	0.625
Peripheral atheroma	166 (7.8)	83 (7.8)	83 (7.8)	>0.999
Ischemic stroke	83 (3.9)	43 (4.0)	40 (3.7)	0.737
Pacemaker	9 (0.4)	5 (0.5)	4 (0.4)	>0.999
Renal failure ^a	42 (2.0)	22 (2.1)	20 (1.9)	0.755
History of hospitalization for HF	135 (6.3)	68 (6.4)	67 (6.3)	0.929
History of hospitalization for AF	155 (7.3)	85 (8.0)	70 (6.6)	0.211
Indications to stress CMR (multiple possible)				
Symptomatic angina	509 (23.9)	236 (22.1)	273 (25.6)	0.060
Dyspnea	301 (14.1)	164 (15.4)	137 (12.8)	0.093
High cardiovascular risk ^b	523 (24.5)	288 (27.0)	235 (22.0)	0.008 ^c
Inconclusive stress test	264 (12.4)	136 (12.7)	128 (12.0)	0.599
Inconclusive CTA ^d	44 (1.7)	31 (2.3)	13 (0.9)	0.042 ^c
PCI or CABG control	579 (27.1)	286 (26.8)	293 (27.5)	0.733
CMR findings				
LVEF, %	56 ± 11	58 ± 9	54 ± 12	<0.001 ^c
LV end-diastolic volume index, mL/m ²	114 ± 34	110 ± 31	119 ± 36	<0.001 ^c
LV end-systolic volume index, mL/m ²	51 ± 25	46 ± 20	56 ± 29	<0.001 ^c
LA end-diastolic volume index, mL/m ²	29 ± 25	27 ± 24	31 ± 25	<0.001 ^c
Presence of ischemia	574 (26.9)	0 (0.0)	574 (53.8)	—
Number of segments of ischemia	0.72 ± 1.66	0.00 ± 0.00	1.43 ± 2.12	—
Presence of LGE with ischemic pattern	617 (28.9)	0 (0.0)	617 (57.8)	—
Number of segments of LGE with ischemic pattern	1.32 ± 1.72	0.00 ± 0.00	2.63 ± 1.56	—
RPP at baseline, mm Hg/beat/min ^e	8.2 (6.7-9.8)	8.2 (6.6-9.8)	8.3 (6.8-10.2)	0.601
RPP at stress, mm Hg/beat/min ^e	9.7 (8.0-11.4)	9.7 (7.9-11.5)	9.8 (8.1-12.3)	0.561
LACI, %	22 ± 18	21 ± 18	23 ± 18	0.033 ^c

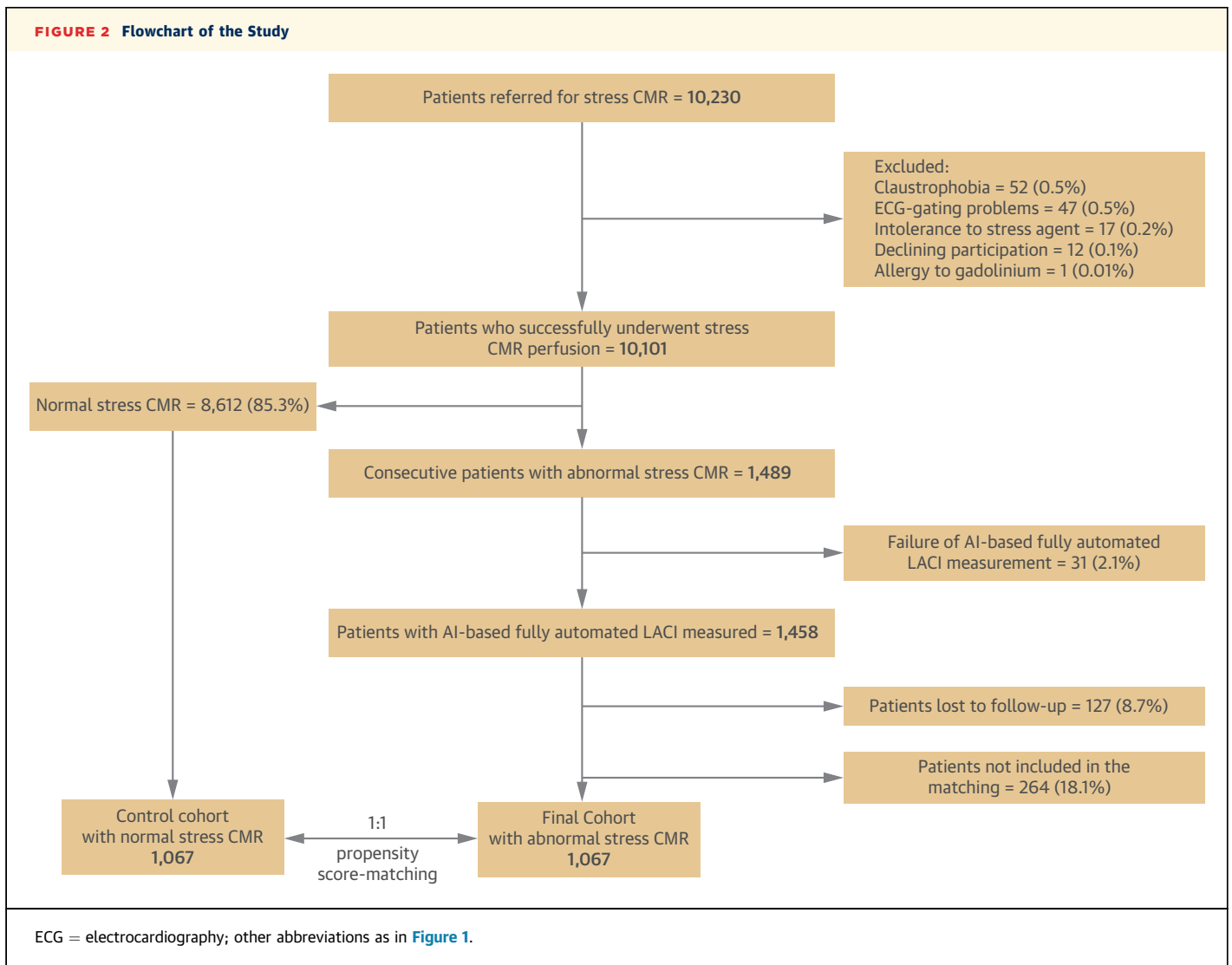
Values are mean ± SD, n (%), or median (IQR). ^aDefined by glomerular filtration rate <60 mL/min/1.73 m². ^bDefined by Framingham Risk Score >20% of risk of CAD at 10 years. ^cStatistically significant with a 2-tailed value of P < 0.05. ^dDefined by coronary stenosis of unknown significance on CTA. ^eRPP = (pressure [mm Hg] × heart rate [beats/min])/1,000.

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; HF = heart failure; LA = left atrial; LACI = left atrioventricular coupling index; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RPP = rate pressure product.

RESULTS

PATIENT CHARACTERISTICS. From the initial cohort of 10,101 consecutive patients who successfully completed the stress CMR study, 1,489 (14.7%) patients had an abnormal stress CMR. Reasons for

failure to complete CMR are detailed in the study flowchart (Figure 2). Among those, AI-based fully automated LACI measurement was performed in 1,458 (97.9%) patients. No patient died during or shortly after CMR, and there were 4 cases of unstable angina. Detailed safety results are presented in the

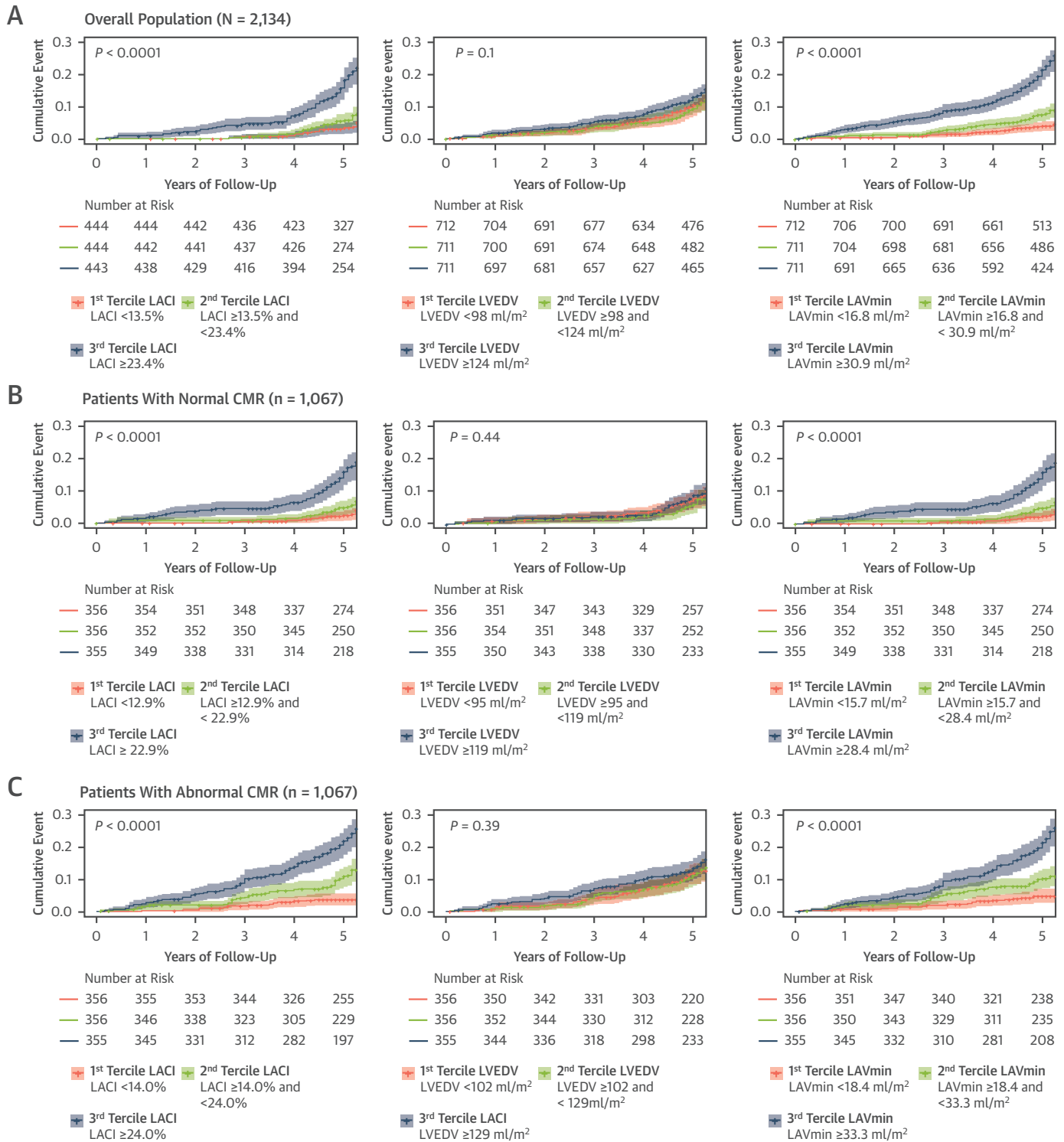


Supplemental Results. Overall, 1,331 (91.3%) patients completed the clinical follow-up. Among those, 1,067 patients were matched using propensity score matching with 1,067 control subjects from the initial cohort who had normal stress CMR. The variables used for propensity score matching were age, sex, obesity, hypertension, diabetes, dyslipidemia, known CAD, history of hospitalization for atrial fibrillation, history of hospitalization for HF, presence of dyspnea, and LVEF. Baseline characteristics of the propensity-matched population ($n = 2,134$) are presented in Table 1. Among these 2,134 patients, 65 (3.0%) had an inadequate hemodynamic response. The mean age of the propensity-matched population was 65 ± 12 years. A total of 77.0% of patients were men, 52.0% had hypertension, 52.0% had dyslipidemia, 30.0% were current or previous smokers, 29.0% had diabetes mellitus, and 10.0% had a family history of CAD. The mean LACI value and LVEF were

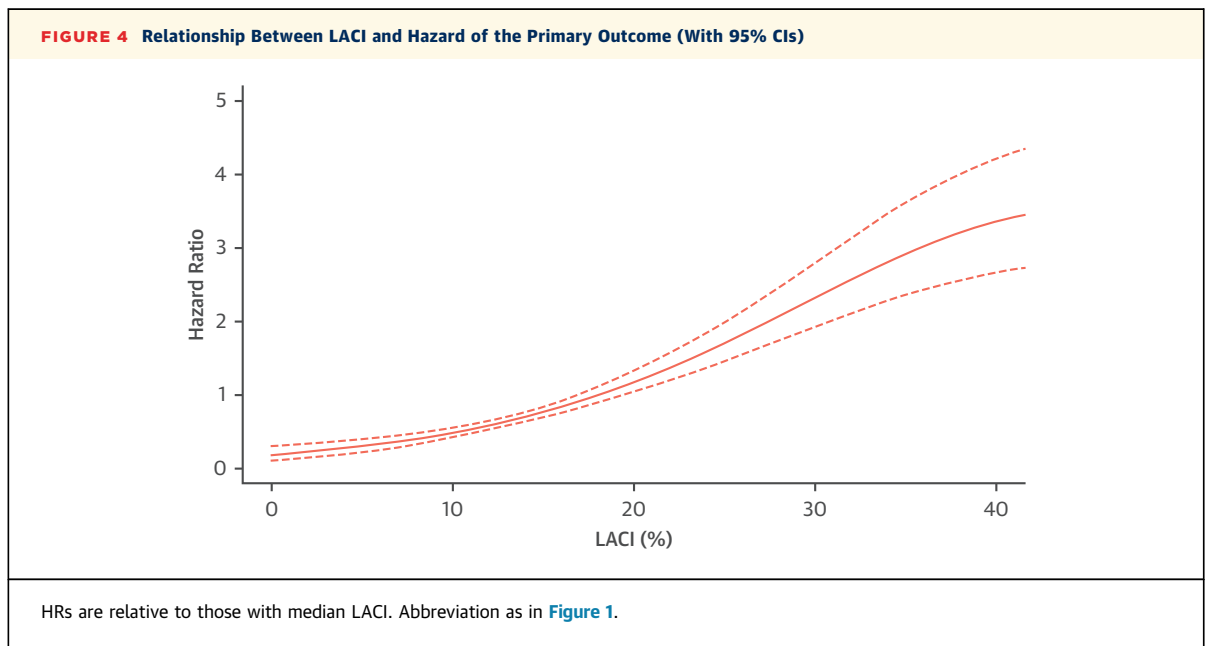
$22 \pm 18\%$ and $56 \pm 10\%$, respectively. Among patients with abnormal CMR, inducible ischemia was detected in 574 (53.8%) patients and LGE with ischemic pattern in 617 (57.8%).

PRIMARY OUTCOME. The median follow-up duration was 5.2 (IQR: 4.8-5.5) years. Of the 2,134 patients, 245 (11.5%) experienced a primary outcome, including 40 (1.9%) cardiovascular deaths and 244 (11.3%) hospitalization for acute HF. Patients who reached the primary endpoint were older with a lower LVEF value and a higher rate of presence of ischemia (all $P < 0.001$) (Supplemental Table 2). The annualized rate of the primary outcome was 9.4% per year. Patients with the lowest LACI value had the lowest annualized rate of primary outcome (2.5% per year for first tercile LACI), whereas the annualized rate of primary outcome was greater for patients with a higher LACI value (7.5% per year for second tercile LACI) and was even higher for patients with the highest LACI value

FIGURE 3 Cumulative Events for the Primary Outcome in the Propensity-Matched Population According to LACI Terciles



Kaplan-Meier curves with CIs of the primary outcome including hospitalization for acute HF or cardiovascular death as a function of length of follow-up stratified by LACI tertiles (A) in the overall propensity-matched population, (B) in those with normal CMR, and (C) in those with abnormal CMR. Tests comparing the 2 groups were based on the log-rank test. HF = heart failure; LAV_{min} = left atrial minimum volume; LVEDV = left ventricular end-diastolic volume index; other abbreviations as in Figure 1.



(18.2% per year for third tercile LACI) (P -trend < 0.001) ([Supplemental Figure 3](#)).

When LACI was categorized in terciles, an LACI value $>23.4\%$ was associated with the primary outcome in comparison with the first tercile ($<13.5\%$; log-rank $P < 0.001$). These findings were homogeneous in the overall propensity-matched population as well as in patients with abnormal and normal CMR (all $P < 0.001$) ([Figure 3](#)). The continuous relationship between LACI and the hazard of the primary outcome is shown in the cubic spline in [Figure 4](#). LACI was positively associated with the primary outcome before and after adjustment for risk factors in the overall propensity-matched population (adjusted HR per 0.1% increment: 1.18; 95% CI: 1.13-1.24), in patients with abnormal CMR (adjusted HR per 0.1% increment: 1.22; 95% CI: 1.14-1.30), and in patients with normal CMR (adjusted HR per 0.1% increment: 1.12; 95% CI: 1.05-1.20) (all $P < 0.001$).

PROGNOSTIC VALUE OF ESTABLISHED CUTOFF.

Using the established prognostic cutoff,¹⁰ an LACI $\geq 25\%$ was independently associated with the occurrence of the primary outcome in the overall propensity-matched population (adjusted HR: 3.27 [95% CI: 2.51-4.26]), in patients with abnormal CMR (adjusted HR: 2.90 [95% CI: 2.09-4.04]), and in patients with normal CMR (adjusted HR: 3.87 [95% CI: 2.49-6.02]; all $P < 0.001$) ([Table 2, Central Illustration](#)). Patients with an LACI $\geq 25\%$ were older, had lower LVEF values, and were more frequently women (all $P < 0.001$) ([Supplemental Table 3](#)). An LACI $\geq 25\%$ was

associated with the occurrence of the primary outcome irrespective of the presence of inducible ischemia or LGE with ischemic pattern ([Supplemental Figure 4](#)). The annualized rates of the primary outcome in patients with an LACI value $\geq 25\%$ are presented in [Supplemental Figure 5](#), stratified by the presence of ischemia or LGE with ischemic pattern. The prognostic value of an LACI $\geq 25\%$ remained consistent in all other subsamples of clinical interest ([Figure 5](#)), such as men and women, patients with or without known CAD, and those with vs without history of hospitalization for HF, regardless of LVEF ([Supplemental Figure 6](#)). In addition, the LACI had similar prognostic value independent of age ([Supplemental Figure 7](#)).

SECONDARY OUTCOMES. After adjustment for traditional risk factors, LACI was also associated with cardiovascular death (HR per 0.1% increment: 1.14 [95% CI: 1.02-1.28]; $P = 0.023$), hospitalization for acute HF (HR per 0.1% increment: 1.19 [95% CI: 1.14-1.25]; $P < 0.001$), and all-cause death (HR per 0.1% increment: 1.11 [95% CI: 1.05-1.19]; $P < 0.001$) ([Supplemental Table 4](#)).

IMPROVEMENT IN RISK PREDICTION WITH ADDITION OF LACI.

In the overall propensity-matched population for the prediction of the primary outcome, C-index values were 0.60 (95% CI: 0.56-0.63) for model 1 with traditional risk factors. The addition of stress CMR findings (LVEF, inducible ischemia, and LGE with ischemic pattern) significantly improved the C-index value to 0.72 (95% CI: 0.69-0.76; C-index improvement for model 1: 0.12; NRI = 0.314; IDI = 0.091; all

TABLE 2 Univariate and Multivariate Analyses of Baseline Characteristics for Prediction of the Primary Composite Outcome

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Overall population (N = 2,134)				
Model 1 ^a : traditional risk factors				
Age	1.03 (1.02-1.04)	<0.001 ^b	1.03 (1.02-1.04)	<0.001 ^b
Male	1.24 (0.92-1.68)	0.151	1.33 (0.99-1.81)	0.062
BMI	0.99 (0.96-1.01)	0.372	0.99 (0.97-1.02)	0.481
Diabetes	0.87 (0.66-1.14)	0.314	0.88 (0.66-1.17)	0.383
Hypertension	0.96 (0.75-1.22)	0.744	1.02 (0.79-1.31)	0.885
Smoking	1.15 (0.89-1.48)	0.290	1.09 (0.84-1.41)	0.498
Dyslipidemia	0.97 (0.77-1.24)	0.829	1.03 (0.80-1.33)	0.817
Known CAD	0.78 (0.61-1.00)	0.050 ^b	0.81 (0.63-1.04)	0.097
History of HF	0.94 (0.59-1.50)	0.786	0.90 (0.56-1.45)	0.667
Model 2 ^c : model 1 + stress CMR				
LVEF, per 10%	0.57 (0.53-0.63)	<0.001 ^b	0.60 (0.55-0.66)	<0.001 ^b
Presence of ischemia	1.98 (1.55-2.54)	<0.001 ^b	2.21 (1.71-2.85)	<0.001 ^b
Presence of LGE with ischemic pattern	1.78 (1.39-2.27)	<0.001 ^b	1.36 (1.07-1.69)	0.041 ^b
Model 3 ^d : model 2 + LACI				
LACI, per 0.1%	1.23 (1.18-1.28)	<0.001 ^b	1.18 (1.13-1.24)	<0.001 ^b
LACI ≥25%	3.90 (3.05-4.99)	<0.001 ^b	3.27 (2.51-4.26)	<0.001 ^b
Model 3 bis ^e : model 2 + LA + LV				
LVEDVI, per 1 mL	1.01 (1.00-1.01)	0.001 ^b	1.00 (0.99-1.00)	0.180
LAVI _{min} , per 1 mL	1.02 (1.01-1.02)	<0.001 ^b	1.01 (1.01-1.01)	<0.001 ^b
Normal CMR population (n = 1,067)				
Model 1 ^a : traditional risk factors				
Age	1.03 (1.01-1.05)	0.002 ^b	1.03 (1.02-1.05)	0.002 ^b
Male	1.49 (0.88-2.52)	0.136	1.48 (0.87-2.52)	0.151
BMI	0.94 (0.90-0.99)	0.010 ^b	0.95 (0.90-1.00)	0.033 ^b
Diabetes	0.70 (0.43-1.14)	0.151	0.79 (0.47-1.32)	0.369
Hypertension	0.90 (0.60-1.35)	0.602	1.11 (0.72-1.71)	0.638
Smoking	1.83 (1.21-2.76)	0.004	1.63 (1.08-2.47)	0.021 ^b
Dyslipidemia	0.79 (0.52-1.18)	0.251	0.90 (0.59-1.39)	0.649
Known CAD	0.79 (0.41-1.22)	0.322	0.66 (0.42-1.02)	0.062
History of HF	0.55 (0.20-1.50)	0.244	0.50 (0.18-1.37)	0.177
Model 2 ^c : model 1 + stress CMR				
LVEF, per 10%	0.54 (0.46-0.63)	<0.001 ^b	0.56 (0.47-0.66)	<0.001 ^b
Model 3 ^d : model 2 + LACI				
LACI, per 0.1%	1.22 (1.15-1.30)	<0.001 ^b	1.12 (1.05-1.20)	<0.001 ^b
LACI ≥25%	4.73 (3.11-7.20)	<0.001 ^b	3.87 (2.49-6.02)	<0.001 ^b
Model 3 bis ^e : model 2 + LA + LV				
LVEDVI, per 1 mL	1.00 (1.00-1.01)	0.197	1.00 (0.99-1.00)	0.562
LAVI _{min} , per 1 mL	1.01 (1.01-1.02)	<0.001 ^b	1.01 (1.01-1.01)	<0.001 ^b

Continued on the next page

$P < 0.001$; LR test $P < 0.001$). Beyond stress CMR findings, the addition of LACI further improved the C-index value to 0.76 (95% CI: 0.73-0.79; C-index improvement for model 1: 0.16; NRI = 0.388; IDI = 0.153; all $P < 0.001$; LR test $P < 0.001$). This additional prognostic value of LACI above traditional risk factors and stress CMR findings for predicting the primary outcome was similar in patients with abnormal and normal stress CMR (Table 3).

In addition, LACI also had better a discrimination and reclassification for the prediction of the primary outcome compared with the multivariable model with

each component of the LACI: LA minimum volume index and the LV end-diastolic volume index (Table 3).

DISCUSSION

In a propensity-matched population of consecutive patients referred for stress CMR, the main findings were: 1) in the overall population, 11.5% reached the primary outcome including hospitalization for acute HF or cardiovascular death after a median follow-up of 5.2 years; 2) AI-based fully automated LACI

TABLE 2 Continued

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Abnormal CMR population (n = 1,067)				
Model 1 ^a : traditional risk factors				
Age	1.03 (1.01-1.04)	<0.001 ^b	1.03 (1.01-1.04)	<0.001 ^b
Male	1.11 (0.77-1.59)	0.579	1.19 (0.82-1.72)	0.365
BMI	1.01 (0.98-1.04)	0.484	1.01 (0.98-1.04)	0.497
Diabetes	0.96 (0.69-1.33)	0.801	0.89 (0.63-1.26)	0.509
Hypertension	0.99 (0.74-1.34)	0.956	0.95 (0.69-1.30)	0.752
Smoking	0.85 (0.61-1.19)	0.351	0.83 (0.59-1.16)	0.276
Dyslipidemia	1.11 (0.82-1.49)	0.514	1.19 (0.86-1.63)	0.294
Known CAD	0.86 (0.63-1.17)	0.335	0.88 (0.65-1.20)	0.433
History of HF	1.18 (0.69-2.01)	0.548	1.18 (0.69-2.03)	0.541
Model 2 ^c : model 1 + stress CMR				
LVEF, per 10%	0.62 (0.56-0.70)	<0.001 ^b	0.62 (0.55-0.70)	<0.001 ^b
Presence of ischemia	1.47 (1.08-2.00)	0.013 ^b	2.93 (1.99-4.32)	<0.001 ^b
Presence of LGE with ischemic pattern	1.24 (0.91-1.69)	0.173	1.84 (1.21-2.79)	0.004 ^b
Model 3 ^d : model 2 + LACI				
LACI, per 0.1%	1.24 (1.18-1.31)	<0.001 ^b	1.22 (1.14-1.30)	<0.001 ^b
LACI ≥25%	3.41 (2.52-4.62)	<0.001 ^b	2.90 (2.09-4.04)	<0.001 ^b
Model 3 bis ^e : model 2 + LA + LV				
LVEDVI, per 1 mL	1.00 (1.00-1.01)	0.037 ^b	1.00 (0.99-1.00)	0.269
LAVI _{min} , per 1 mL	1.02 (1.01-1.02)	<0.001 ^b	1.01 (1.01-1.02)	<0.001 ^b

^aCovariates in model 1 (traditional HF risk factors): age, male sex, BMI, diabetes, hypertension, smoking, dyslipidemia, known CAD, and history of HF. ^bStatistically significant with a 2-tailed value of $P < 0.05$. ^cCovariates in model 2 (stress CMR): model 1 + LVEF value, presence of inducible ischemia, and presence of LGE. ^dCovariates in model 3 (LACI): model 2 with LACI value. ^eCovariates in model 3 bis (LVEDVI + LAVI_{min}): model 2 with LVEDVI and LAVI_{min} values.

LAVI_{min} = left atrial minimum volume index; LVEDVI = left ventricular end-diastolic volume index; other abbreviations as in Table 1.

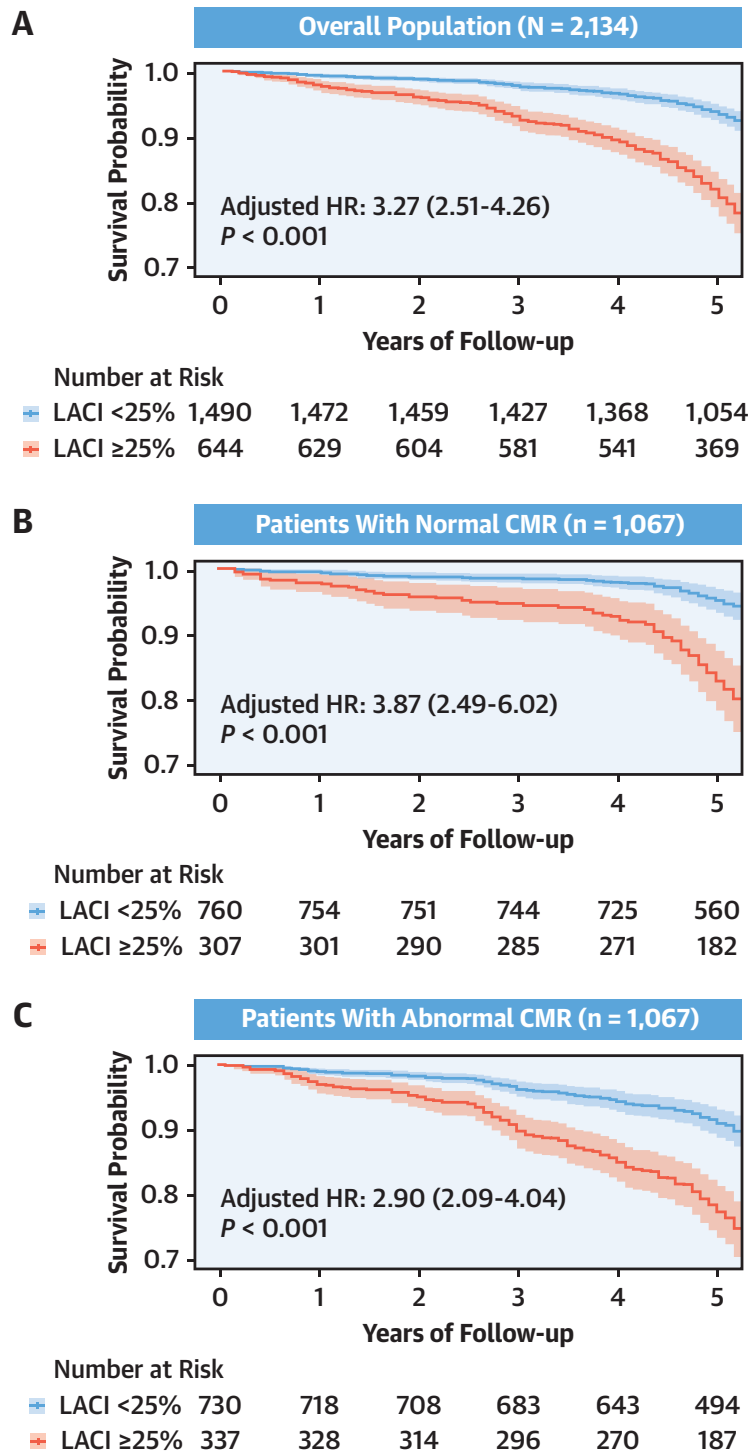
measurement was feasible in 98.0% of patients referred for stress CMR with good accuracy; 3) LACI was independently associated with the primary outcome in patients with abnormal and normal stress CMR; 4) LACI improved discrimination and reclassification beyond traditional HF risk factors and stress CMR findings including presence of inducible ischemia or LGE with ischemic pattern; and 5) LACI had a better discrimination and reclassification compared with the multivariable model with each component of the LACI: LA minimum volume index and LV end-diastolic volume index.

LACI AS AN INDEPENDENT PROGNOSTIC MARKER DURING STRESS CMR. Several studies have underlined the strong prognostic value of inducible ischemia and LGE with ischemic pattern by stress CMR to predict the occurrence of acute HF and cardiovascular death.³⁻⁵ Impaired left atrioventricular coupling, indicated by a greater LACI value, was independently associated with the primary outcome (hospitalization for acute HF or cardiovascular death) in patients with normal and abnormal stress CMR. In addition, LACI improved model discrimination and reclassification in predicting the risk of events above traditional HF risk factors through fast unsupervised

fully automated AI-based measurements. Our study suggests that LACI could identify an earlier stage of LA remodeling when compared with LA volume alone, exhibiting a higher prognostic value for predicting outcomes after adjustment for covariates. Thus, relating LA to LV volume, LACI improves model discrimination and reclassification in predicting the risk of cardiovascular events relative to such individual parameters measured separately. In line with prior reports from MESA,^{10,12,13} such findings emphasize the important interaction that exists between LA and LV performance, particularly during LV diastole.

The LACI was independently associated with HF outcomes and improved model discrimination and reclassification in patients with normal stress CMR. These results are consistent with a prior study from MESA in 4,124 healthy individuals without cardiovascular disease that reported an incremental prognostic value of LACI in predicting incident HF and cardiovascular death.^{10,12} Using the survival tree method, the best cutoff of LACI for the prediction of the primary outcome was 26.2%. This finding is consistent with the cutoff of 25% previously derived from MESA.¹⁰ While the annualized event rate of HF

CENTRAL ILLUSTRATION Adjusted Event-Free Survival Curves for the Primary Outcome Stratified by LACI



Pezel T, et al. J Am Coll Cardiol Img. 2023;■(■):■-■.

The adjusted event-free survival curves with CIs were determined with the final model including all traditional heart failure risk factors (age, male sex, body mass index, diabetes, hypertension, smoking, dyslipidemia, known coronary artery disease, history of heart failure, left ventricular ejection fraction value, presence of inducible ischemia, presence of late gadolinium enhancement, and left atrioventricular coupling index [LACI] value) (A) in the overall propensity-matched population, (B) in those with normal cardiac magnetic resonance (CMR), and (C) in those with abnormal CMR.

FIGURE 5 Subgroup Analysis of the Prognostic Value of LACI on the Primary Outcome in the Propensity-Matched Cohort

Subgroup	LACI <25% N _{event} /N _{subgroup}	LACI ≥25% N _{event} /N _{subgroup}	HR (95% CI)	P-Value	Interaction P-Value
Age					
<65 years	55/800 (6.9%)	44/174 (25.3%)	4.29 (2.88-6.38)	< 0.001	0.978
≥65 years	52/690 (7.5%)	114/470 (24.5)	3.6 (2.59-5)	< 0.001	
Sex					
Female	17/315 (5.4%)	37/182 (20.3%)	4.2 (2.36-7.47)	< 0.001	0.898
Male	90/1175 (7.7%)	121/462 (26.2%)	3.97 (3.02-5.22)	< 0.001	
Obesity					
No	85/1114 (7.6%)	123/487 (25.3%)	3.83 (2.9-5.05)	< 0.001	0.793
Yes	22/376 (5.9%)	35/157 (22.3%)	4.2 (2.46-7.16)	< 0.001	
Diabetes					
No	85/1046 (8.5%)	109/463 (23.5%)	3.85 (2.94-5.03)	< 0.001	0.816
Yes	22/444 (5.0%)	49/181 (27.1%)	4.16 (2.56-6.77)	< 0.001	
Hypertension					
No	56/716 (7.8%)	76/310 (24.5%)	3.49 (2.47-4.92)	< 0.001	0.382
Yes	51/774 (6.6%)	82/334 (24.6%)	4.38 (3.08-6.22)	< 0.001	
Smoking					
No	69/1044 (6.6%)	108/455 (23.7%)	4.12 (3.05-5.58)	< 0.001	0.609
Yes	38/446 (8.5%)	50/189 (26.5%)	3.52 (2.31-5.37)	< 0.001	
Known CAD					
No	63/856 (7.4%)	103/391 (26.3%)	3.99 (2.91-5.46)	< 0.001	0.814
Yes	44/634 (6.9%)	55/253 (21.7%)	3.61 (2.42-5.36)	< 0.001	
Symptomatic					
No	68/951 (7.2%)	99/414 23.9%	3.88 (2.84-5.28)	< 0.001	0.908
Yes	39/539 (7.2%)	59/230 25.7%	3.86 (2.58-5.79)	< 0.001	
History of HF					
No	102/1391 (7.3%)	144/608 (23.7%)	3.66 (2.84-4.71)	< 0.001	0.087
Yes	5/99(5.1%)	14/36 (38.9%)	9.6 (3.45-26.7)	< 0.001	
LVEF					
≥ 50 %	63/1191 (5.3%)	71/471 (15.1%)	3.15 (2.24-4.42)	< 0.001	0.179
< 50 %	44/299 (14.7%)	87/173 (50.3%)	4.33 (3.01-6.23)	< 0.001	
Ischemia					
No	60/1090 (5.5%)	100/470 (21.3%)	4.43 (3.21-6.1)	< 0.001	0.286
Yes	47/400 (11.8%)	58/174 (33.3%)	3.25 (2.21-4.78)	< 0.001	
LGE					
No	64/1083 (5.9%)	91/434 (21.0%)	4.04 (2.93-5.57)	< 0.001	0.833
Yes	43/407 (10.6%)	67/210 (31.9%)	3.41 (2.52-4.62)	< 0.001	
CMR					
Normal	35/760 (4.6%)	58/307 (18.9%)	4.73 (3.11-7.2)	< 0.001	0.232
Abnormal	72/730 (9.9%)	100/337 (29.7%)	3.41 (2.52-4.62)	< 0.001	

Forest-plot with unadjusted HR (black squares) and 95% CIs (horizontal lines) of the primary outcome including hospitalization for acute HF or cardiovascular death in subgroups of the overall propensity-matched cohort. Interactions between the tested variables and the effects of LACI on the primary outcome were determined using the heterogeneity test with P value interaction. N events indicates the number of patients who died, and N subgroup indicates number of patients in the subgroup. CAD = coronary artery disease; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; other abbreviations as in Figures 1 and 3.

outcomes is low in patients with normal stress CMR, patients with normal stress CMR and an LACI value ≥25% had a much higher annualized rate of HF outcomes (14.0% per year) than patients with an LACI value <25% (3.0% per year). The prognostic value of an LACI ≥25% remained consistent regardless of age,

in patients with or without known CAD and irrespective of LVEF.

Whereas the LACI was initially evaluated in individuals without cardiovascular disease, a recent study showed its strong prognostic value for incident atrial fibrillation in patients with hypertrophic

TABLE 3 Discrimination and Reclassification Associated With CMR Parameters to Predict the Primary Composite Outcome

	C-Index (95% CI)	Chi-Square Test	NRI	IDI	LR Test
Overall population (N = 2,134)					
Model 1 ^a	0.60 (0.56-0.63)	33.55		Ref.	<0.001
Model 2 ^b : model 1 + stress CMR	0.72 (0.69-0.76)	190.21	0.314	0.091	<0.001
Model 3 ^c : model 2 + LACI	0.76 (0.73-0.79)	252.49	0.388	0.153	<0.001
Model 2 + LVEDVI	0.72 (0.69-0.75)	192.00	0.307	0.094	<0.001
Model 2 + LVEDVI + LACI	0.76 (0.73-0.79)	257.22	0.390	0.155	<0.001
Model 2 + LAVI _{min}	0.75 (0.72-0.78)	231.16	0.343	0.109	<0.001
Model 2 + LAVI _{min} + LACI	0.77 (0.74-0.80)	295.92	0.444	0.176	<0.001
Normal CMR population (n = 1,067)					
Model 1 ^a	0.66 (0.61-0.72)	33.55		Ref.	<0.001
Model 2 ^b : model 1 + stress CMR	0.71 (0.66-0.77)	74.30	0.278	0.075	<0.001
Model 3 ^c : model 2 + LACI	0.75 (0.70-0.81)	103.46	0.337	0.102	<0.001
Model 2 + LVEDVI	0.71 (0.65-0.77)	74.65	0.251	0.098	<0.001
Model 2 + LVEDVI + LACI	0.75 (0.70-0.81)	108.34	0.339	0.104	<0.001
Model 2 + LAVI _{min}	0.74 (0.68-0.79)	88.60	0.307	0.091	<0.001
Model 2 + LAVI _{min} + LACI	0.76 (0.70-0.81)	121.22	0.359	0.108	<0.001
Abnormal CMR population (n = 1,067)					
Model 1 ^a	0.59 (0.55-0.64)	19.53		Ref.	0.02
Model 2 ^b : model 1 + stress CMR	0.70 (0.65-0.74)	109.56	0.265	0.098	<0.001
Model 3 ^c : model 2 + LACI	0.73 (0.69-0.78)	167.50	0.323	0.139	<0.001
Model 2 + LVEDVI	0.70 (0.65-0.74)	110.77	0.278	0.102	<0.001
Model 2 + LVEDVI + LACI	0.73 (0.69-0.78)	169.21	0.341	0.141	<0.001
Model 2 + LAVI _{min}	0.72 (0.68-0.76)	132.41	0.298	0.111	<0.001
Model 2 + LAVI _{min} + LACI	0.74 (0.69-0.78)	209.77	0.339	0.152	<0.001

^aCovariates in model 1 (traditional HF risk factors): age, male sex, BMI, diabetes, hypertension, smoking, dyslipidemia, known CAD, and history of HF. ^bCovariates in model 2 (stress CMR): model 1 + LVEF value, presence of inducible ischemia, and presence of LGE. ^cCovariates in model 3 (LACI): model 2 with LACI value \geq 25%.
 IDI = integrative discrimination index; LR = likelihood ratio; NRI = net reclassification improvement; Ref. = reference; other abbreviations as in Tables 1 and 2.

cardiomyopathy.²⁵ The current study reports an independent prognostic value of LACI to predict HF outcomes in patients with either inducible ischemia or LGE with ischemic pattern on stress CMR. Consistently, the prognostic value of LACI was persistent in patients with LVEF <50%, known CAD, and history of hospitalization for HF.

INCREMENTAL PROGNOSTIC VALUE OF LACI ABOVE STRESS CMR FINDINGS. The LACI improved model discrimination and reclassification beyond traditional HF risk factors and stress CMR findings, including inducible ischemia or LGE with ischemic pattern. These findings may be explained by the fact that the primary outcome was mostly represented by hospitalizations for HF, rather than by MI or cardiovascular death. These data may have implications for improved primary and secondary prevention of patients in stage A or B of HF.⁹ Indeed, the incremental prognostic value of LACI could help tailor prevention strategies in the patients at higher risk of HF.

STUDY LIMITATIONS. First, 8.7% patients were lost to follow-up, which can be explained by the relatively long follow-up period and study design. However, the

French National Registry of Death has been carefully reviewed, which strengthens the data on death. Second, complete patient follow-up to measure the occurrence of the primary outcome was performed only for the propensity score-matched population. Third, baseline and follow-up data for medications were not collected in the study. Consistently, the potential consequences on outcomes of the changes in decision making due to stress CMR could not be collected in this retrospective study. As previously reported,¹⁰ the LACI was determined using 2-dimensional cine long-axis views for measurements of LA volumes, which may have underestimated actual volumes by 10% to 20%.²⁶ However, this method has been validated in clinical studies and has been shown to be suitable for large sample size studies.²⁷ Regarding the comparison of LACI with other LA parameters, LA strain was not measured in this study. While the proportion of patients with known CAD, dyslipidemia, and obesity were variables included in the creation of the propensity score, the propensity score matching performed did not allow a balanced distribution of these variables between the 2 groups. Although recent studies highlight the

prognostic value of quantitative stress perfusion analysis during a CMR stress exam, this study did not perform such a quantitative perfusion sequence. Finally, dipyridamole was used as the vasodilator agent mainly because of medico-economic reasons with very similar efficacy/safety profile compared with adenosine.

CONCLUSIONS

In consecutive patients referred for stress CMR, an impaired LACI was independently associated with the occurrence of hospitalization for acute HF and cardiovascular death during a median follow-up of 5.2 years. The prognostic value of LACI was consistent in patients with abnormal and normal stress CMR. The addition of LACI to risk prediction models including stress CMR findings (ischemia or LGE) improved model discrimination and reclassification for HF outcomes. Future studies should validate these findings to better understand the role of left atrioventricular coupling in HF pathophysiology.

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Drs Toupin, Dr Chitiboi, Ms Jacob, and Dr Sharma are employees of Siemens Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In consecutive patients referred for stress CMR, an impaired LACI was independently associated with the occurrence of hospitalization for acute HF and cardiovascular death. This prognostic value of LACI was consistent in both patients with abnormal and normal stress CMR. Furthermore, LACI improved model discrimination and reclassification to predict HF events above traditional risk factors and stress CMR findings through fast unsupervised fully automated AI-based measurements.

TRANSLATIONAL OUTLOOK: Further prospective studies are needed to validate these findings and test whether a wider use of fully automated LACI measurement could help to guide the management and decision making of our patients in clinical routine.

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KEY WORDS cardiovascular death, cardiac magnetic resonance, coupling, heart failure, left atrioventricular coupling index, myocardial ischemia, stress testing

APPENDIX For expanded Methods and Results sections as well as supplemental figures, tables, and references, please see the online version of this paper.

Partie 8 :

Étude n°7 : Mesure du LACI par scanner cardiaque

Left atrioventricular coupling index assessed using cardiac CT as a prognostic marker of cardiovascular death

Pezel, T ; Dillinger JG, Toupin S, Mirailles R, Logeart D, Cohen-Solal A, Unger A, Canuti ES, Beauvais F, Lafont A, Gonçalves T, Lequipar A, Gall E, Boutigny A, Ah-Sing T, Hamzi L, Lima JAC, Bousson V, Henry P

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Après avoir étudié la valeur pronostique de la valeur de notre index de couplage auriculo-ventriculaire gauche, le LACI, avec une mesure réalisée par IRM cardiaque (études n°1 à 6), cette septième étude se propose d'investiguer la faisabilité et l'impact pronostique de la mesure du LACI par scanner cardiaque. Sachant que l'accès au scanner cardiaque est beaucoup plus facile que celui de l'IRM cardiaque, cette étude n°7 sera dans la continuité de l'étude n°6, une piste importante pour soutenir le développement et la diffusion de notre nouvel indice en routine clinique quotidienne.

Ainsi, l'objectif de cette étude n°7 du travail de thèse d'étudier la valeur pronostique du LACI mesuré par scanner cardiaque, pour prédire la mortalité cardiovasculaire au sein d'une cohorte française monocentrique au sein du CHU Lariboisière (APHP, Paris) de patients consécutifs adressés pour un coroscanner. Entre 2010 et 2020, nous avons mené une

étude monocentrique avec tous les patients consécutifs sans maladie cardiovasculaire connue adressés en scanner cardiaque sur le CHU de Lariboisière (APHP, Paris). Le LACI a été défini comme le rapport entre les volumes télédiastoliques de l'oreillette gauche et du ventricule gauche. Le critère de jugement principal était le décès cardiovasculaire. Des régressions de Cox ont été utilisées pour évaluer l'association entre le LACI et le critère de jugement principal après ajustement pour les facteurs de risque traditionnels et les résultats traditionnels obtenus à partir du coroscaner.

Chez 1444 patients (âge moyen, 70 ± 12 ans ; 43% d'hommes), 67 (4,3 %) patients ont présenté un décès cardiovasculaire après un suivi médian de 6,8 ans. Après ajustement, le LACI était positivement associé à la survenue de décès d'origine cardiovasculaire (HR 1,07 ; IC à 95 % [1,05–1,09]; $p < 0,001$) et à la mortalité toutes causes confondues (HR 1,05 ; IC à 95 % [1,03-1,07]; $p < 0,001$). Après ajustement, un LACI ≥ 25 % a montré la meilleure amélioration de la discrimination et de la reclassification du modèle pour prédire la mort cardiovasculaire au-dessus des facteurs de risque traditionnels et des résultats de la TDM cardiaque (amélioration du C-index : 0,27 ; amélioration du NRI = 0,826 ; amélioration de l'IDI = 0,209, tous $p < 0,001$). Ainsi, le LACI mesuré par scanner cardiaque est indépendamment associé à la mort cardiovasculaire et à la mort toutes causes confondues chez les patients sans maladie cardiovasculaire connue référés pour scanner cardiaque, avec une valeur pronostique supplémentaire par rapport aux facteurs de risque traditionnels.

En résumé, cette étude n°7 d'une cohorte de patients consécutifs sans maladie cardiovasculaire connue référés pour un coroscaner au sein du CHU de Lariboisière (APHP, Paris) a montré les principaux résultats suivants : (i), 4,3 % des patients ont présenté un décès CV après un suivi médian de 6,8 ans ; (ii), les reproductibilités intra- et inter-lecteurs de la mesure du LACI par scanner cardiaque étaient bonnes ; (iii), le LACI était indépendamment

associé à la mort cardiovasculaire chez les patients après ajustement pour les facteurs de risque traditionnels et les résultats du coroscanner ; (iv), le LACI a amélioré la discrimination et la reclassification au-delà des facteurs de risque traditionnels et des résultats du coroscanner pour prédire la survenue d'un décès cardiovasculaire; et (v), le LACI avait une meilleure discrimination et reclassification par rapport au modèle multivarié incluant chaque composante du LACI (volumes télédiastolique de l'oreillette gauche et du ventricule gauche séparément). À notre connaissance, cette septième étude est la première à montrer la bonne faisabilité de la mesure LACI à l'aide d'images de scanner cardiaque, ainsi que sa valeur pronostique incrémentale au-delà des facteurs de risque cliniques traditionnels et des résultats classiquement obtenus par le coroscanner.



Original article

Left atrioventricular coupling index assessed using cardiac CT as a prognostic marker of cardiovascular death

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ABSTRACT

Purpose: The purpose of this study was to investigate the prognostic value of left atrioventricular coupling index (LACI) assessed by cardiac computed tomography (CT), to predict cardiovascular death in consecutive patients referred for cardiac CT with coronary analysis.

Materials and methods: Between 2010 and 2020, we conducted a single-centre study with all consecutive patients without known cardiovascular disease referred for cardiac CT. LACI was defined as the ratio of left atrial to left ventricle end-diastolic volumes. The primary outcome was cardiovascular death. Cox regressions were used to evaluate the association between LACI and primary outcome after adjustment for traditional risk factors and cardiac CT angiography findings.

Results: In 1,444 patients (mean age, 70 ± 12 [standard deviation] years; 43% men), 67 (4.3%) patients experienced cardiovascular death after a median follow-up of 6.8 (Q1, Q3: 5.9, 9.1) years. After adjustment, LACI was positively associated with the occurrence of cardiovascular death (adjusted hazard ratio [HR], 1.07 [95% CI: 1.05–1.09] per 1% increment; $P < 0.001$), and all-cause death (adjusted HR, 1.05 [95% CI: 1.03–1.07] per 1% increment; $P < 0.001$). After adjustment, a LACI $\geq 25\%$ showed the best improvement in model discrimination and reclassification for predicting cardiovascular death above traditional risk factors and cardiac CT findings (C-statistic improvement: 0.27; Nnet reclassification improvement = 0.826; Integrative discrimination index = 0.209, all $P < 0.001$; likelihood-ratio-test, $P < 0.001$).

Conclusion: LACI measured by cardiac CT is independently associated with cardiovascular death and all-cause death in patients without known cardiovascular disease referred for cardiac CT, with an incremental prognostic value over traditional risk factors and cardiac CT findings.

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Abbreviations: CI, Confidence interval; CMR, Cardiovascular magnetic resonance; CCTA, Cardiac CT angiography; CT, Computed tomography; CV, Cardiovascular; CVD, Cardiovascular disease; HR, Hazard ratio; IDI, Integrative discrimination index; LACI, Left atrioventricular coupling index; LR, Likelihood-ratio; LV, Left ventricular; LVEF, Left ventricular ejection fraction; MESA, Multi-ethnic atherosclerosis study; NRI, Nnet reclassification improvement; SD, Standard deviation

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1. Introduction

Cardiovascular mortality is the leading cause of death worldwide [1]. For early detection of high-risk individuals, several studies have highlighted the importance of assessing left ventricular (LV) and left atrial (LA) function by cardiovascular magnetic resonance (CMR) [2–5]. Beyond this assessment of LV and LA parameters measured separately, the close physiological relationship between LA and LV suggests that the evaluation of left atrioventricular coupling could be a better predictor of cardiovascular disease (CVD) than any LA or LV parameter [6,7].

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In a recent study from the Multi-Ethnic Study of Atherosclerosis (MESA), our group showed the prognostic value of a novel left atrioventricular coupling index (LACI) defined by the LA end-diastolic volume divided by the LV end-diastolic volume using CMR [8]. Those prior findings suggested that an increase in LACI was associated with cardiovascular outcomes [8]. More recently, using a longitudinal analysis between two CMR examinations, our group has also shown the incremental prognostic value of annualised change in LACI above traditional risk factors to predict incident heart failure, and incident atrial fibrillation over 10 years. LACI had a better prognostic value than individual changes in LA or LV parameters measured separately [9–11]. All these results support the physiological concept of left atrioventricular coupling.

Although CMR is the gold standard for assessment of cardiac volumes, its accessibility in clinical routine is limited compared with other techniques such as cardiac computed tomography (CT) and echocardiography. Furthermore, it is interesting to note that the current guidelines recommend acquisition usually around 75% of the cardiac cycle phase (close to the end-diastolic phase) for cardiac CT with coronary analysis [12,13]. As LACI is based on end-diastolic volumes, it can therefore be easily measured on standard cardiac CT angiography (CCTA). However, its prognostic value using cardiac CT images has not been investigated yet.

Therefore, the purpose of this study was to investigate the prognostic value of the LACI assessed by cardiac CT, to predict the occurrence of cardiovascular death in consecutive patients without known CVD referred for cardiac CT with coronary analysis.

2. Materials and methods

2.1. Study population

A single-center longitudinal study with retrospective enrolment of all consecutive patients without known CVD referred for cardiac CT with coronary analysis in our CT laboratory of Lariboisiere University Hospital was conducted between January 2010 and December 2020. To exclude all patients with known CVD, main exclusion criteria were: (i), known stenosis $\geq 50\%$ on at least one epicardial coronary artery on prior invasive coronary angiography or cardiac CT; (ii), patients with a positive functional test; (iii), patients with a history of revascularization (defined by previous percutaneous coronary intervention or coronary artery bypass graft); (iv), patients with prior myocardial infarction; (v), history of atrial fibrillation; (vi), history of peripheral atheroma disease; (vii), significant valvular disease; (viii), prior hospitalisation for heart failure; and (ix), known LV dysfunction (defined by LV ejection fraction [LVEF] $< 50\%$). In addition, all patients with allergy to iodine and glomerular filtration rate < 30 mL/min/1.73m² were excluded. Clinical data were collected according to medical history and clinical examination on the day of cardiac CT examination, and exclusion criteria were checked through the medical records. All patients provided informed written consent. The study was approved by the local Ethic Committee of our Institutions and conducted in accordance with the 1964 Declaration of Helsinki. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

2.2. Patient follow-up and outcomes

The primary outcome was the occurrence of CV death defined as sudden cardiac death with documented fatal arrhythmias, or any death immediately preceded by acute myocardial infarction, acute or exacerbation of heart failure, or stroke. All these clinical events were defined according to the published standardized definitions [14]. The identification of dead patients was performed using the electronic French National Registry of Death. Data

collection ended in June 2022. Clinical event adjudication was based on the follow-up clinical visit or contact, with a consensus reached by two senior cardiologists.

2.3. Cardiac CT protocol and analysis

Concerning the cardiac CT protocol, CT was performed using: (i), a 64-row multidetector CT scanner (Sensation 64, Siemens Healthcare) between 2010 and 2016; (ii), a 80-row multidetector CT scanners (Aquilion Prime CT scanner, Toshiba Medical Systems, or Somatom Definition Edge, Siemens Healthcare) between 2016 and 2020. Imaging protocols complied to the Society of Cardiovascular Computed Tomography guidelines on appropriateness and performance of cardiac CT available at the time of scanning [15]. Regarding the acquisition, the retrospective mode or prospective mode with padding and dose adaptation was used to measure the LVEF value. Concerning the radiation exposure, the dose-length product (DLP), defined as the total radiation energy absorbed by the patient's body, was individually reported from each cardiac CT in mSv/mGy.cm. The effective radiation dose was calculated as the product of the dose-length product times a conversion coefficient for the chest ($K = 0.014$ mSv/mGy.cm). In this study, the mean DLP was 739 ± 197 (standard deviation [SD]) mGy/cm, which was equivalent to 10.3 ± 2.8 (SD) mSv.

Cardiac CT volumes were interpreted using multi-planar reconstruction and maximum intensity projections, according to the 16-segment coronary artery model [16]. Coronary segments were scored visually for the presence and composition of coronary plaque and degree of luminal stenosis. In each coronary segment, coronary atherosclerosis was defined as any tissue structure >1 mm either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, and the vessel lumen itself [17]. In each coronary segment, plaques were classified as noncalcified, calcified, or mixed, as previously defined [18,19]. Following the CAD-RADSTM 2.0 classification, the severity of CAD was categorized according to the highest value of stenosis of the diameter amongst each segment: normal (0% luminal stenosis), non-obstructive CAD (1–49% luminal stenosis), obstructive CAD (50–69% luminal stenosis) or severe obstructive CAD ($\geq 70\%$ luminal stenosis) [13]. Cardiac CT findings were further divided as 1-, 2-, or 3-vessel disease/left main obstructive CAD according to the number of major epicardial vessels with $\geq 50\%$ stenosis. Presence of stenosis $\geq 50\%$ in the left main coronary artery was considered as a 3-vessel disease equivalent. The numbers of segments with any plaque or stenosis, a specific plaque composition, a specific luminal stenosis, or a specific topography of the plaque (proximal or not) were assessed for each patient [18,20]. Left ventricular ejection fraction (LVEF) was measured according to current guidelines, using the true LV volume with the “cardiac function” module of the Syngo.via software (Siemens Healthcare) [21]. Using a random sample of 50 patients, inter-rater reliability for the diagnosis of obstructive CAD on cardiac CT was excellent (unweighted Cohen κ , 0.82; 95% CI: 0.74–0.88).

2.4. Left atrioventricular coupling index

LACI was defined as the ratio between the LA end-diastolic volume and the LV end-diastolic volume (Fig. 1) [8]. The LA and the LV volumes were measured from the two- and four-chamber views using the biplane Simpson's method, as previously described (Syngo.via software, Siemens Healthcare) [8]. The LA and LV volumes were measured in the same end-diastolic phase defined by the largest LV volume (Table 1). The identification of the end-diastolic phase was done after analysis of the entire cardiac cycle using the reconstructions each 5% of the RR interval. All cardiac CT measurements were determined by two independent physicians (T. A.-S. and T.G., with six and four years of experience, respectively) who were blinded to

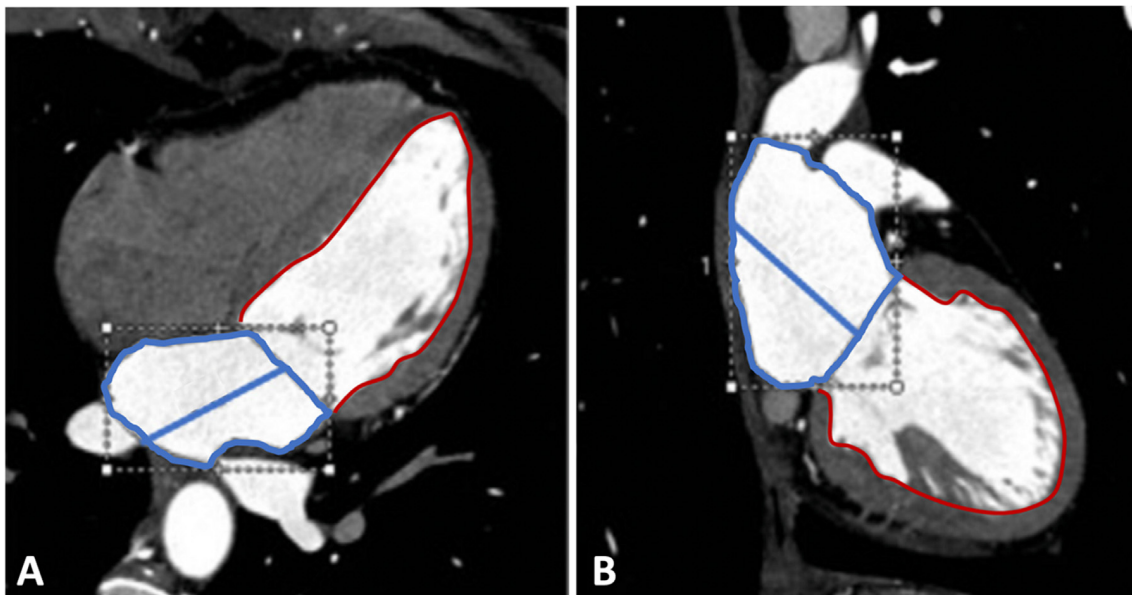


Fig. 1. Left atrioventricular coupling index (LACI) measurement method using cardiac CT.

Example of the left atrium (LA, blue line) and left ventricle (LV, red line). LA and LV segmentation in a 69-year-old man with diabetes, hypertension and dyslipidemia, presenting atypical angina to assess LACI by cardiac computed tomography (CT) defined by the ratio between the LA end-diastolic volume and the LV end-diastolic volume from long-axis cine images: 4-chamber (A) and 2-chamber (B) views.

echocardiographic measurements or clinical parameters; when a difference $\geq 5\%$ was found, a third reader (T.P., with six years of experience) was asked to give a final opinion that was used for the final analysis. LACI value was expressed as a percentage and a higher LACI indicates a greater disproportion between LA and LV volumes during LV end diastole, reflecting greater impairment of left atrioventricular coupling [8,9]. Using the survival tree method in the current study, the LACI was transformed into a binary variable using the cut-off of 25.3%.

2.5. Statistical analysis

Continuous variables were expressed as mean \pm SD, categorical variables as frequency with percentage, and follow-up as median and interquartile range (IQR; Q1, Q3) [22]. Comparison of patient characteristics used the Mann-Whitney test for continuous variables and the Pearson Chi-square for categorical variables. Survival probabilities of the primary outcome were estimated using the Kaplan-Meier method and the survival curves compared with the log-rank test. Data of patients who were lost to follow-up were censored at the time of the last contact. Cox proportional hazards methods were used to identify the predictors of the primary outcome. The proportional hazard assumption was visually assessed using Schoenfeld

residuals. Martingale residuals were used to detect nonlinearity in continuous variables.

To assess the incremental prognostic value of LACI, different multivariable models were used for adjustment: (i), model 1 (traditional cardiovascular risk factors): adjustment for traditional risk factors at baseline including age, male, diabetes, hypertension, smoking, dyslipidaemia; (ii), model 2 (cardiac CT model): model 1 + LVEF (per 5% increase in LVEF), number of segments with stenosis $>70\%$, number of segments with noncalcified plaques, and number of vessels with obstructive CAD; and (iii), model 3 (LACI model): model 2 + LACI value. The discriminative capacity of each model for predicting the primary outcome was determined according to the Harrell's C-statistic before and after addition of LACI. The additional predictive value of the LACI value was calculated by the Harrell's C-statistic increment, integrative discrimination index (IDI), continuous net reclassification improvement (NRI), global chi-square and likelihood-ratio (LR) test.

As sensitivity analysis, we also performed multivariable model including covariates by stepwise variable selection with entry and exit criteria set at the $P < 0.05$ level. Forest plots were obtained, where interactions between the tested variables and the effects of LACI on the occurrence of the primary outcome were determined using a partial likelihood ratio test. Comparison tests to assess a dose-effect relationship between the LACI value and the occurrence of CV death were based on the Cochran-Armitage test for trend. A two-tailed $P < 0.05$ was considered statistically significant. Statistical analysis was performed using R software, version 3.6.0 (R Project for Statistical Computing).

3. Results

3.1. Patient characteristics

From the initial cohort of 6982 consecutive patients who successfully completed the cardiac CT study with coronary analysis, 1498 (21.5%) patients had no known CVD. Reasons for failure to complete cardiac CT are detailed in the study flowchart (Fig. 2). Overall, 1444 patients (96.4%) completed the clinical follow-up and constituted the

Table 1
Methodology of left atrium measurements by cardiac CT.

To calculate the LACI, the minimum left atrium volume (LAVmin) was measured during the end-diastolic phase using the area-length method from apical 2- and 4-chamber views, using the following formula for biplane calculation: LA volume = $\frac{0.0848 \times \text{area4ch} \times \text{area2ch}}{\sqrt{\frac{\text{length4ch} + \text{length2ch}}{2}}}$. LAVmin was indexed to the body surface area (ml/m^2). The LA volume variables were defined as follows:

- LA end-systolic volume (maximum LA volume): before mitral valve opening.
- LA end-diastolic volume (minimum LA volume): after mitral valve closure.

LA cycle has been described in three phases, a reservoir collecting pulmonary venous flow during ventricular systole, a conduit for passage of blood into the left ventricle during early diastole and a booster pump by augmenting ventricular filling during late diastole via atrial contraction.

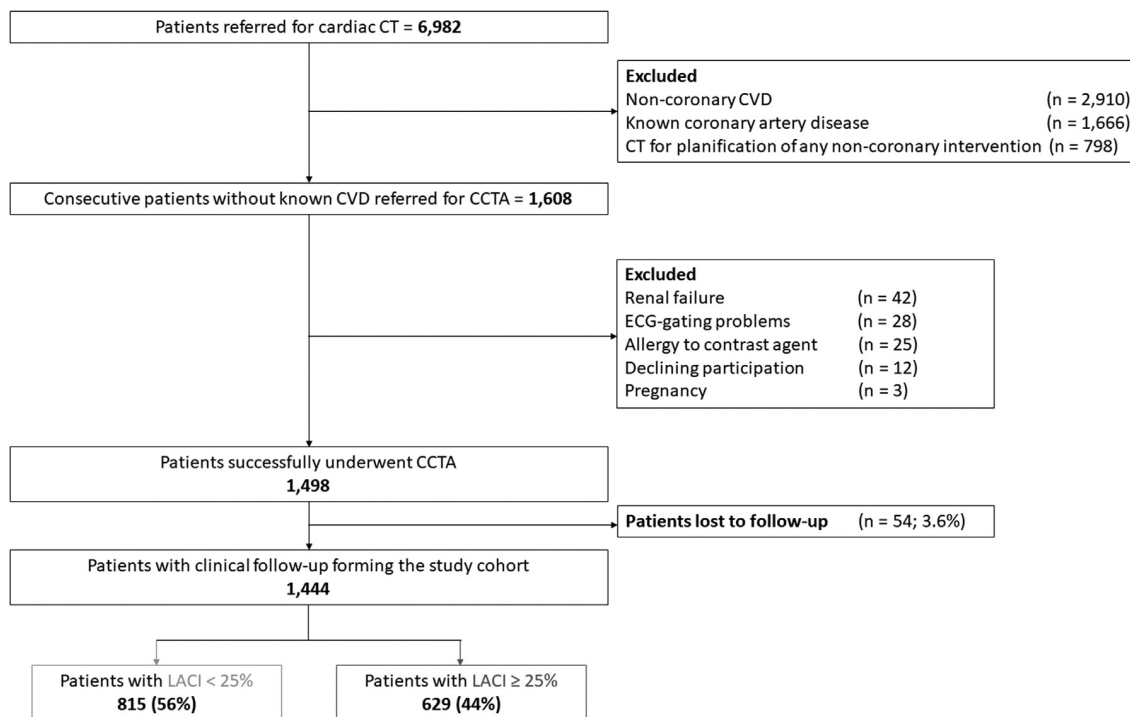


Fig. 2. Study flowchart

Non-coronary cardiovascular death was defined by history of atrial fibrillation, history of peripheral atheroma disease, significant valvular disease, prior hospitalisation for heart failure, and known left ventricle dysfunction with LV ejection fraction < 50%.

CVD: cardiovascular disease; CCTA: coronary computed tomography angiography; ECG: electrocardiogram; LACI: left atrioventricular coupling index.

final cohort. Baseline characteristics of the study population are presented in Table 2. The mean age of the study population was 70 ± 12 (SD) years. Forty three percent of patients were men, 67% had hypertension, 51% dyslipidaemia, 33% diabetes mellitus, 29% had a family history of CAD, and 20% were active smokers. Of the 1444 patients, 916 (63%) were symptomatic with chest pain and 528 (37%) were asymptomatic but with >2 cardiovascular risk factors. On cardiac CT, 73% of patients had no obstructive CAD, 22% had 1-vessel CAD, and 5% had 2 or 3/LM-vessel CAD. The mean LACI value and LVEF were 26 ± 12 (SD) % and 56 ± 9 (SD) %, respectively.

3.2. Intra- and inter-reader reproducibilities of the LACI measurement using cardiac CT

The intra- and inter-reader reproducibilities of the LACI were good with intraclass correlation of 0.91 (95% CI: 0.87–0.95) and intraclass correlation of 0.80 (95% CI: 0.69–0.89), respectively. Using a random sample size of 60 patients, we also performed threshold based 3D segmentation method, which makes no geometric assumptions with an excellent intraclass correlation of 0.93 (95% CI: 0.88–0.98) compared with the biplane Simpson’s method.

3.3. Outcomes

The median follow-up duration was 6.8 years (Q1, Q3: 5.9, 9.1 years). Of the 1444 patients, 92 (6.4%) patients experienced all-cause death, including 67 (4.6%) patients with CV death. Patients who reached CV death were older with a higher rate of males, diabetes, hypertension and dyslipidaemia (all $P < 0.05$) (Table 3). The annualised all-cause death and CV death rates were 3.2%/year and 2.3%/year, respectively. Patients with the lowest LACI value had the lowest annualised CV death rate (0.1%/year for 1st tercile LACI), whereas the annualised CV death rate was greater for patients with a higher LACI

value (1.5%/year for 2nd tercile LACI), and even higher for patients with the highest LACI value (5.5%/year for 3rd tercile LACI, P -trend < 0.001). Before and after adjustment for risk factors, LACI was positively associated with the occurrence of CV death (adjusted hazard ratio [HR], 1.07 [95% CI: 1.05–1.09] per 1% increment; $P < 0.001$) (Table 4) and all-cause death (adjusted HR, 1.05 [95% CI: 1.03–1.07] per 1% increment; $P < 0.001$). As sensitivity analysis using a model including covariables by stepwise variable selection, LACI remained independently associated with CV death (adjusted HR, 1.08 [95% CI: 1.06–1.11] per 1% increment; $P < 0.001$).

3.4. Prognostic value of established LACI cut-off

Using the established prognostic cut-off [8], a LACI ≥25% was independently associated with the occurrence of CV death (adjusted HR, 40.3 [95% CI: 9.74–167]) ($P < 0.001$) (Table 4 and Fig. 3). Patients with LACI ≥25% had a lower LVEF value ($P = 0.013$), a greater number of vessels with obstructive CAD ($P = 0.027$), and a greater number of segments with non-calcified or mixed plaques ($P = 0.002$ and $P = 0.006$, respectively) (Table 2). Patients with the LACI value < 25% had the lowest annualised CV death rate (0.1%/year), whereas the annualised CV death rate was greater for patients with LACI value ≥25% (5.2%/year; $P < 0.001$). The prognostic value of a LACI ≥25% remained consistent in all other subsamples of clinical interest (Fig. 4), and the prognostic value of LACI does not change according to these characteristics such as age, gender, diabetes status, presence of obstructive CAD, and LVEF value (all $P \geq 0.05$) (Fig. 5).

3.5. Improvement in risk prediction with addition of LACI

For the prediction of CV death, C-statistic values were 0.68 (95% CI: 0.61–0.75) for the model with traditional risk factors (model 1). The addition of cardiac CT findings (model 2) significantly improved

Table 2
Baseline and CCTA characteristics of patients according to LACI values (N = 1444).

	All patients (n = 1444)	LACI < 25% (n = 815)	LACI ≥ 25% (n = 629)	P value
Age (years)	70 ± 12	70 ± 12	70 ± 12	0.439
Males	616 (42.7%)	355 (43.6%)	261 (41.5%)	0.432
Body mass index (kg/m ²)	28.4 ± 4.5	28.3 ± 4.4	28.4 ± 4.6	0.658
Coronary risk factors				
Diabetes mellitus	481 (33.3%)	255 (31.3%)	226 (35.9%)	0.064
Hypertension	967 (67.0%)	536 (65.8%)	431 (68.5%)	0.270
Obesity*	382 (26.5%)	209 (25.6%)	173 (27.5%)	0.427
Dyslipidemia	736 (51.0%)	415 (50.9%)	321 (51.0%)	0.966
Active smoker	281 (19.5%)	146 (17.9%)	135 (21.5%)	0.091
Family history of CAD	425 (29.4%)	234 (28.7%)	191 (30.4%)	0.494
Renal failure†	12 (0.8%)	10 (1.2%)	2 (0.3%)	0.059
Cardiac CT findings				
Patient with at least one stenosis >50%	388 (26.9%)	195 (23.9%)	193 (30.7%)	<0.001
Patient with at least one stenosis >70%	158 (10.9%)	82 (10.1%)	76 (12.1%)	0.028
No. of segments with stenosis >70%	0.09 ± 0.29	0.08 ± 0.28	0.10 ± 0.30	0.311
No. of proximal segments with stenosis >50%	0.14 ± 0.36	0.13 ± 0.36	0.14 ± 0.36	0.770
No. of proximal segments with stenosis >70%	0.07 ± 0.26	0.06 ± 0.24	0.08 ± 0.27	0.298
No. of segments with non-calcified plaques	0.36 ± 0.69	0.32 ± 0.66	0.42 ± 0.73	0.002
No. of segments with mixed plaques	0.31 ± 0.57	0.27 ± 0.55	0.35 ± 0.60	0.006
No. of segments with calcified plaques	0.30 ± 0.65	0.29 ± 0.64	0.32 ± 0.65	0.086
Number of vessels with obstructive CAD				0.027
0-vessel	1056 (73.1%)	620 (76.1%)	436 (69.3%)	
1-vessel	310 (21.5%)	156 (19.1%)	154 (24.5%)	
2-vessel	50 (3.5%)	23 (2.8%)	27 (4.3%)	
3-vessel or LM	28 (1.9%)	16 (2.0%)	12 (1.9%)	
LV ejection fraction (%)	56 ± 9	57 ± 9	56 ± 9	0.013
LV end-diastolic volume index, (mL/m ²)	114 ± 31	118 ± 29	1108 ± 32	<0.001
LA end-diastolic volume index, (mL/m ²)	29 ± 15	21 ± 7	39 ± 15	<0.001
LACI (%)	26 ± 12	18 ± 4	36 ± 9	<0.001

Values are n (%), mean ± standard deviation, or median (interquartile range).

BMI: body mass index; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CV: cardiovascular; LA: left atrium; LACI: left atrio-ventricular coupling index; LM: left main artery; LV: left ventricle; SD: standard deviation.

* defined by BMI ≥ 30 kg/m².

† defined by glomerular filtration rate between 60 and 90 mL/min/1.73 m².

Table 3
Baseline and Cardiac CT characteristics of patients according to cardiovascular death (N = 1444).

	All patients (n = 1444)	No cardiovascular death (n = 1377)	Cardiovascular death (n = 67)	P value
Age (years)	70 ± 12	70 ± 12	74 ± 11	0.018
Males	616 (42.7%)	579 (42.0%)	37 (55.2%)	0.033
Body mass index (kg/m ²)	28.4 ± 4.5	28.4 ± 4.4	27.7 ± 5.4	0.074
Coronary risk factors				
Diabetes mellitus	481 (33.3%)	443 (32.2%)	38 (56.7%)	<0.001
Hypertension	967 (67.0%)	914 (66.4%)	53 (79.1%)	0.031
Obesity*	382 (26.5%)	369 (26.8%)	13 (19.4%)	0.180
Dyslipidemia	736 (51.0%)	691 (50.2%)	45 (67.2%)	0.007
Smoking	281 (19.5%)	269 (19.5%)	12 (17.9%)	0.743
Family history of CAD	425 (29.4%)	397 (28.8%)	28 (41.8%)	0.023
Renal failure†	12 (0.8%)	11 (0.8%)	1 (1.5%)	0.436
Cardiac CT findings				
No. of segments with stenosis >70%	0.09 ± 0.29	0.08 ± 0.28	0.22 ± 0.42	<0.001
No. of proximal segments with stenosis >50%	0.14 ± 0.36	0.12 ± 0.34	0.39 ± 0.55	<0.001
No. of proximal segments with stenosis >70%	0.07 ± 0.26	0.06 ± 0.24	0.19 ± 0.40	<0.001
No. of segments with non-calcified plaques	0.36 ± 0.69	0.32 ± 0.66	1.31 ± 0.72	<0.001
No. of segments with mixed plaques	0.31 ± 0.57	0.26 ± 0.53	1.18 ± 0.67	<0.001
No. of segments with calcified plaques	0.30 ± 0.65	0.27 ± 0.62	0.96 ± 0.81	<0.001
Number of vessels with obstructive CAD				<0.001
0-vessel	1056 (73.1%)	1056 (76.7%)	0 (0.0%)	<0.001
1-vessel	310 (21.5%)	257 (18.7%)	53 (79.1%)	
2-vessel	50 (3.5%)	44 (3.2%)	6 (9.0%)	
3-vessel or LM	28 (1.9%)	20 (1.5%)	8 (11.9%)	
LV ejection fraction (%)	56 ± 9	57 ± 9	53 ± 10	<0.001
LV end-diastolic volume index (mL/m ²)	114 ± 31	113 ± 30	122 ± 38	0.089
LA end-diastolic volume index (mL/m ²)	29 ± 15	28 ± 14	46 ± 22	<0.001
LACI (%)	26 ± 12	25 ± 11	37 ± 10	<0.001
LACI ≥ 25%	629 (43.6%)	564 (41.0%)	65 (97.0%)	<0.001

Values are n (%), mean ± standard deviation, or median (interquartile range).

BMI: body mass index; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CV: cardiovascular; LA: left atrium; LACI: left atrio-ventricular coupling index; LM: left main artery; LV: left ventricle; SD: standard deviation.

* defined by BMI ≥ 30 kg/m².

† defined by glomerular filtration rate between 60 and 90 mL/min/1.73 m².

Table 4
Univariable and multivariable analyses of baseline characteristics for prediction of cardiovascular death.

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Model 1[*]: Traditional risk factors				
Age	1.03 (1.01–1.05)	0.007	1.03 (1.01–1.06)	0.006
Male	1.67 (1.03–2.71)	0.036	1.60 (0.98–2.61)	0.058
Diabetes	2.60 (1.60–4.22)	<0.001	2.31 (1.40–3.83)	0.001
Hypertension	1.92 (1.06–3.46)	0.030	1.40 (0.76–2.58)	0.284
Smoking	0.92 (0.49–1.72)	0.790	0.89 (0.47–1.69)	0.721
Dyslipidemia	2.01 (1.21–3.35)	0.007	1.74 (1.03–2.93)	0.038
Model 2[†]: Model 1 + Cardiac CT				
LVEF, per 5%	0.79 (0.70–0.90)	<0.001	0.91 (0.78–1.07)	0.273
Number of segments with stenosis >70%	2.95 (1.66–5.24)	<0.001	1.27 (0.68–2.39)	0.451
Number of segments with noncalcified plaques	3.35 (2.70–4.14)	<0.001	2.30 (1.74–3.03)	<0.001
Number of vessels with obstructive CAD	3.57 (2.90–4.39)	<0.001	2.73 (2.10–3.56)	<0.001
Model 3[‡]: Model 2 + LACI				
LACI, %	1.07 (1.06–1.09)	<0.001	1.07 (1.05–1.09)	<0.001
LACI ≥ 25%	43.8 (10.7–179)	<0.001	40.3 (9.74–167)	<0.001
Model 2 + LVEDVi	1.01 (1.00–1.02)	0.023	1.01 (1.00–1.02)	0.017
Model 2 + LAVimin	1.05 (1.04–1.06)	<0.001	1.05 (1.04–1.06)	<0.001

* Covariables in the **model 1** (traditional risk factors): age, male, diabetes, hypertension, smoking, dyslipidemia.

† Covariables in the **model 2** (cardiac CT): model 1 + LVEF, per 5%, Number of segments with stenosis >70%, Number of segments with noncalcified plaques, and Number of vessels with obstructive CAD.

‡ Covariables in the **model 3** (LACI): model 2 with LACI value.

the C-statistic value to 0.91 (95% CI: 0.89–0.93; C-statistic improvement for “model 2[†]”: 0.23; NRI = 0.782; IDI = 0.143, all $P < 0.001$; LR-test, $P < 0.001$). Beyond cardiac CT findings, the addition of LACI further improved the C-statistic value to 0.95 (95% CI: 0.94 - 0.96; C-statistic improvement for “model 1^{*}”: 0.27; NRI = 0.826; IDI = 0.209, all $P < 0.001$; LR-test, $P < 0.001$) (Fig. 6). This additional prognostic

value of LACI above traditional risk factors and cardiac CT findings was similar to predict all-cause death (Table 5). In addition, LACI also had better a discrimination and reclassification for the prediction of CV death compared with the multivariable model with each component of the LACI: LA end-diastolic volume indexed (LAVimin) to the LV end-diastolic volume indexed (LVEDVi) (Table 5).

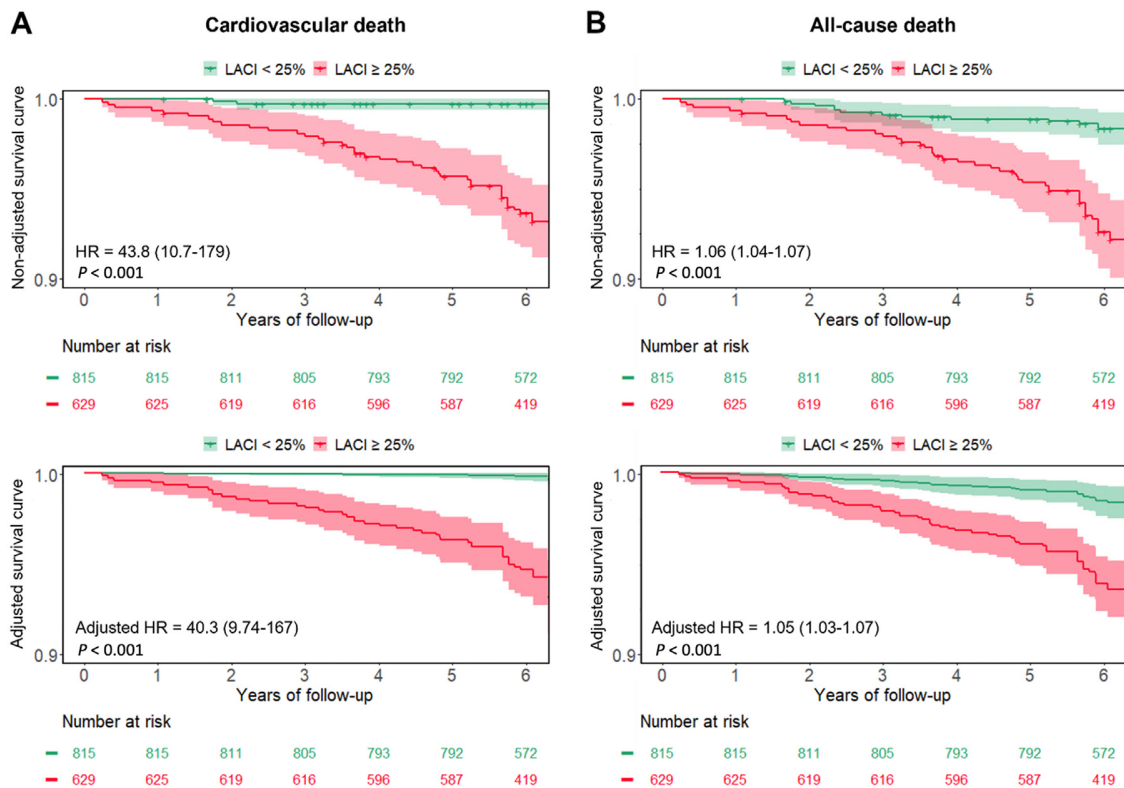


Fig. 3. Event-free survival curves for cardiovascular death or all-cause death stratified by left atrioventricular coupling index (LACI). The adjusted event-free survival curves with confidence intervals were determined with the final multivariable model (age, male, diabetes, hypertension, smoking, dyslipidemia, left ventricle ejection fraction (LVEF) per 5%, number of segments with stenosis >70%, number of segments with noncalcified plaques, number of vessels with obstructive coronary artery disease (CAD), and LACI value stratified by the best cut-off). HR indicates hazard ratio.

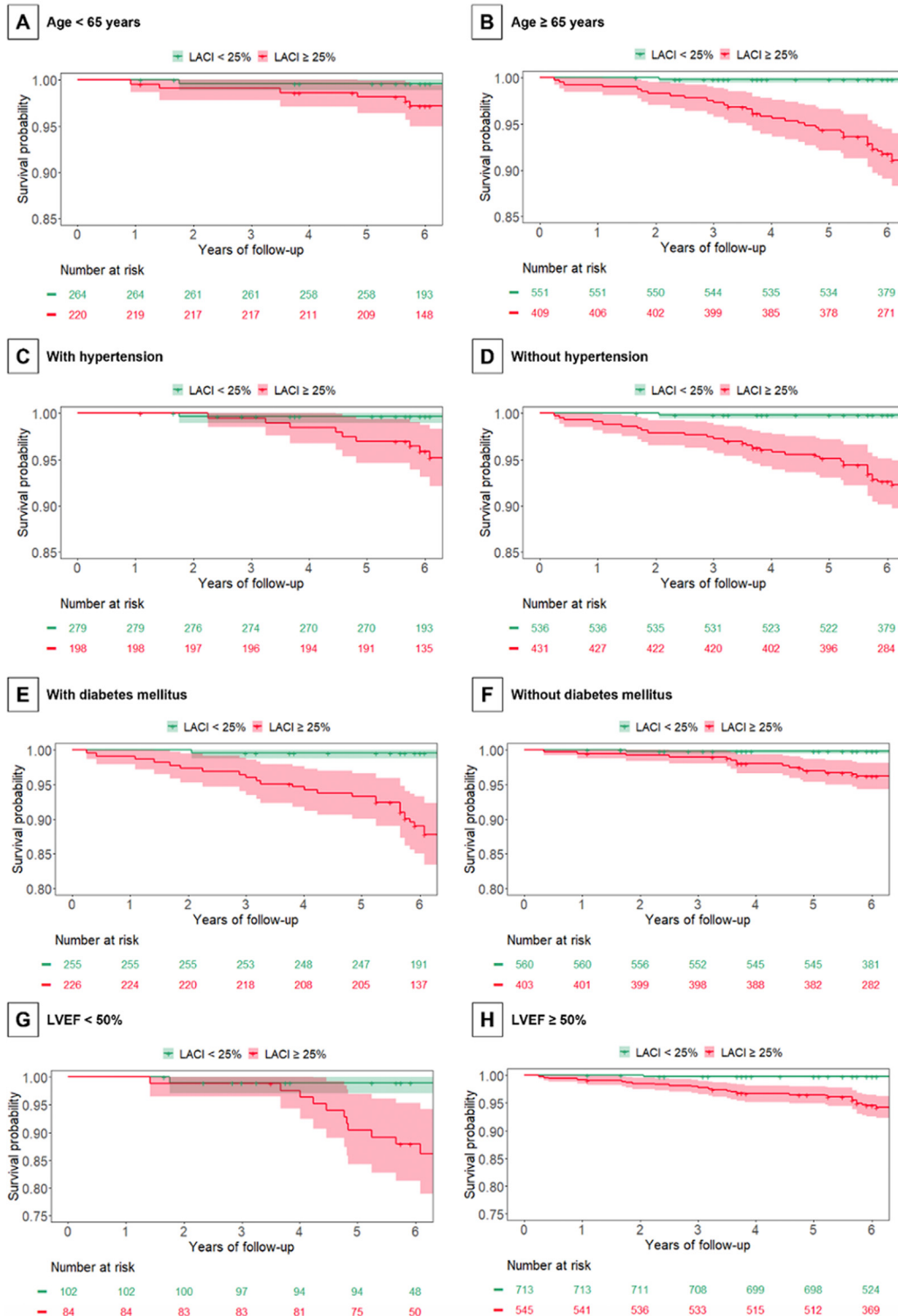


Fig. 4. Event-free survival curves for cardiovascular death stratified by left atrioventricular coupling index (LACI) in subgroups of clinical interest.

4. Discussion

In a cohort of consecutive patients without known CVD referred for cardiac CT with coronary analysis, the main findings are: (i), 4.3% of patients experienced CV death after median follow-up of 6.8 years; (ii), the intra- and inter-reader reproducibilities of the LACI

measurement using cardiac CT were good; (iii), LACI was independently associated with CV death in patients after adjustment for traditional risk factors and cardiac CT findings; (iv), LACI improved discrimination and reclassification beyond traditional risk factors and cardiac CT findings to predict the occurrence of CV death; and (v), LACI had a better discrimination and reclassification compared

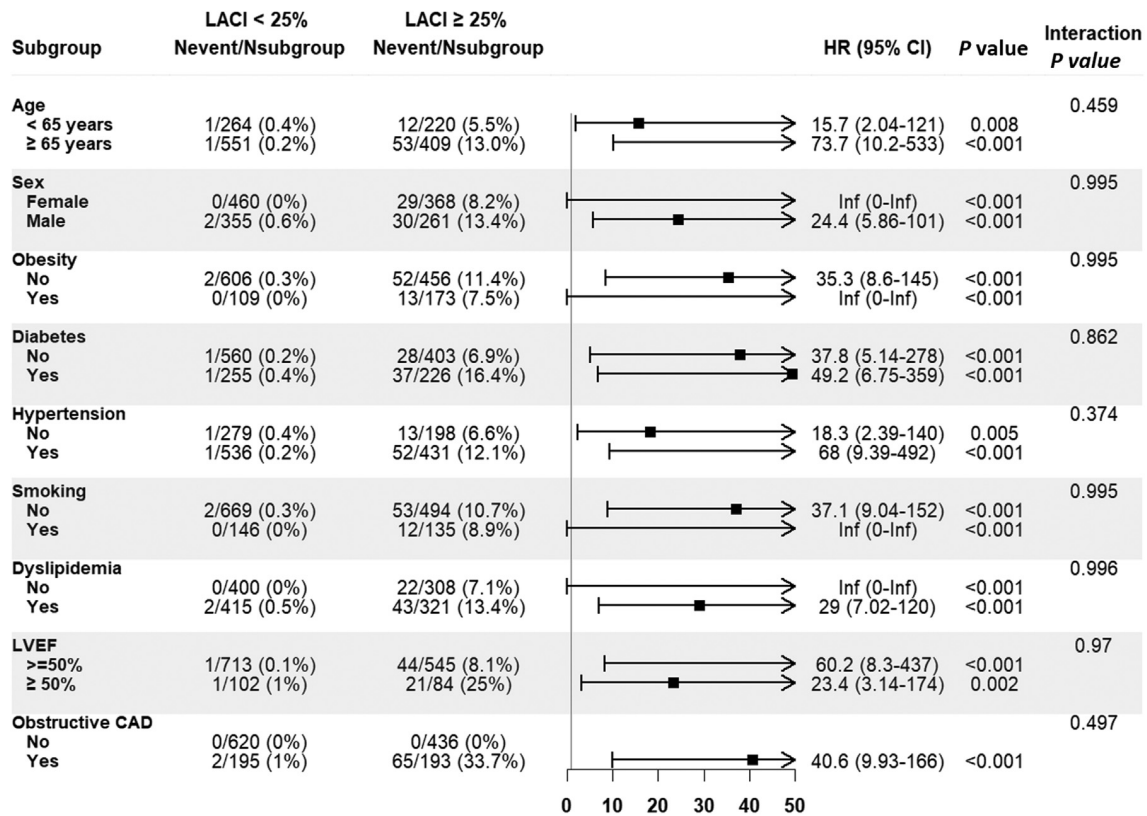


Fig. 5. Forest-plot: Subgroup analysis of the prognostic value of left atrioventricular coupling index (LACI) on cardiovascular death. Forest-plot with unadjusted hazard ratio (black squares) and 95% confidence interval (CI, horizontal lines) of cardiovascular (CV) death in subgroups of the overall cohort. Interactions between the tested variables and the effects of LACI on CV death were determined using the heterogeneity test with P-value interaction. *N events/N subgroup: number of patients who died / number of patients in the subgroup.

with the multivariable model with each component of the LACI (LA end-diastolic and LV end-diastolic volumes indexed). To our knowledge, the feasibility of the LACI measurement using cardiac CT images, and its incremental prognostic value over and above traditional clinical risk factors and cardiac CT findings have not been previously reported.

Our working group has recently described a novel left atrioventricular coupling index measured by CMR from the MESA study, the LACI, as an independent prognostic marker of CV outcomes exhibiting a better discrimination and reclassification compared to any LA or LV parameter [8]. These findings were then confirmed by several other studies from MESA also showing the interest of the annualised change in LACI to predict CV outcomes [9,10]. Notably, the concept of left AV coupling is complex and the LACI does not capture all the complexity and granularity of this left AV coupling. Although these results using CMR to measure LACI seems robust and relevant, access to CMR examinations remains limited in daily practice, especially for primary prevention patients. Therefore, it could be useful to evaluate the feasibility and prognostic value of the LACI measured with more accessible imaging modalities such as echocardiography or cardiac CT. To address this issue, Meucci et al. have recently confirmed the strong prognostic value of LACI measured using echocardiography to predict outcomes in patients with hypertrophic cardiomyopathy [11]. Knowing that LACI measurement is performed in end-diastole [8,23], it is important to emphasize that current recommendations for cardiac CT protocol, recommend acquisition usually around 75% of the cardiac cycle phase (close to the end-diastolic phase) [12,13]. While it is common practice in cardiac imaging to measure the maximum LA volume during the end-systolic phase to assess LV filling pressures, this study measures the minimum LA volume during the

end-diastolic phase to stratify the risk of outcomes. Thus, LACI could be easily measured on all cardiac CT with coronary analysis exams regardless of the prospective or retrospective mode of acquisition with excellent spatial resolution for LA and LV volume measurement. To our knowledge, the current study is the first to describe good feasibility of measuring LACI from cardiac CT images with good intra- and inter-reader reproducibilities.

Several studies have underlined the strong prognostic value of cardiac CT findings based on the degree of stenosis, plaque analysis or plaque burden to predict the occurrence of death [24,25,26]. However, apart from LVEF value, no LA or LV structural or functional parameter is used in the final cardiac CT report in clinical routine to stratify the risk of CV events. In the current study assessing patients without known CVD, the LACI was independently associated with CV and all-cause death, and improved model discrimination and reclassification above traditional risk factors. These results are consistent with prior study from MESA in 4,124 healthy participants without CVD that reported an incremental prognostic value of LACI measured by CMR in predicting CV death [8]. Using the survival tree method in the current CCTA study, the best cut-off of LACI for the prediction of CV death was 25.3%. This finding is consistent with the cut-off of 25% previously derived from MESA [8].

All these results suggest that LACI may, by identifying an earlier stage of LA remodelling compared with LA volume alone, show a better prognostic value to predict outcomes after adjustment for traditional risk factors [23]. Therefore, relating LA to LV volume, LACI improves model discrimination and reclassification in predicting the risk of CV death and all-cause death relative to such individual parameters measured separately. In accordance with prior studies from MESA, such findings underline the important interaction that

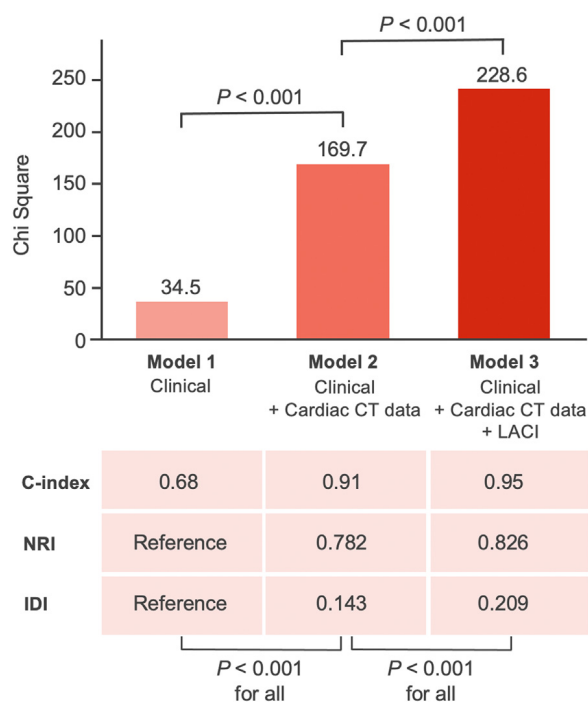


Fig. 6. Discrimination and reclassification associated with cardiac CT parameters and left atrioventricular coupling index value to predict cardiovascular death.

Covariables in the model 1 (traditional risk factors) were: age, male, diabetes, hypertension, smoking, dyslipidemia. Covariables in the model 2 (cardiac CT) were: model 1 + LVEF (per 5% increase in LVEF), Number of segments with stenosis >70%, Number of segments with noncalcified plaques, and Number of vessels with obstructive CAD. Covariables in the model 3 (LACI) were: model 2 with LACI value per 1%.

IDI indicates integrative discrimination index ; NRI indicates continuous net reclassification improvement.

exists between LA and LV performances, particularly during LV diastole [8,9,10,23].

The LACI improved model discrimination and reclassification beyond traditional risk factors and cardiac CT findings, including LVEF value, number of segments with stenosis >70%, number of

segments with noncalcified plaques, and number of vessels with obstructive CAD. These data may have implications for improved primary CVD prevention. Indeed, the incremental prognostic value of LACI could help tailor prevention strategies in the patients at higher risk of CVD. Future larger multicentre studies will have to validate this interest of measuring LACI in clinical routine during a cardiac CT examination.

Our study has some limitations. First, 3.6% patients were lost to follow-up, which can be explained by the relatively long follow-up and the design of the study. However, the French National Registry of Death has been carefully reviewed, which strengthens the data on mortality. Second, baseline and follow-up data for medications were not collected in the study. Consistently, the potential consequences on outcomes of the changes in decision-making due to cardiac CT could not be collected in this retrospective study. However, all patients with obstructive CAD on cardiac CT received optimal medical treatment including statins, in the absence of contraindications or significant side effects according to the current guidelines [27]. As previously reported, the LACI was determined using 2-dimensional long axis reconstructions for measurements of both LA and LV volumes, which may have underestimated true volumes by 11.5–20% [8,28]. However, this method has been validated in clinical studies and is suitable for large sample size [29]. Non-invasive fractional flow reserve CT was not performed because of unavailability during the study period. Because the coronary artery calcium score was not systematically performed prior to cardiac CT, we do not have sufficient statistical power to carry out a dedicated analysis to compare LACI to coronary artery calcium score. Cardiac CT assessment was mainly based on the degree of stenosis, as plaque analysis or plaque burden were not included in the final model.

In conclusion, in consecutive patients without known CVD referred for cardiac CT with coronary analysis with a relatively low prevalence of obstructive CAD detected, an impaired left atrioventricular coupling index measured by cardiac CT was independently associated with the occurrence of CV death after a median follow-up of 6.8 years. The addition of LACI to risk prediction models including traditional risk factors and cardiac CT findings improved the prognostic value to predict CV death. Future studies should validate these findings to better define the role of left atrioventricular coupling assessment using CT in clinical routine.

Table 5
Discrimination and reclassification associated with cardiac CT parameters to predict all-cause death and cardiovascular death.

	C-index (95% CI)	Chi-square	NRI (95% CI)	IDI (95% CI)	LR test
Cardiovascular death					
Model 1*	0.68 (0.61–0.75)	34.5	Reference		Reference
Model 2†: Model 1 + cardiac CT	0.91 (0.89–0.93)	169.7	0.782 (0.540–0.830)	0.143 (0.095–0.245)	P<0.001
Model 3‡: Model 2 + LACI	0.95 (0.94–0.96)	228.6	0.826 (0.681–0.869)	0.209 (0.152–0.337)	P<0.001
Model 2 + LAV _i min	0.93 (0.91–0.95)	198.9	0.799 (0.598–0.802)	0.177 (0.122–0.360)	P<0.001
Model 2 + LVEDVi	0.92 (0.90–0.93)	177.2	0.802 (0.558–0.849)	0.143 (0.095–0.245)	P<0.001
All-cause death					
Model 1*	0.72 (0.66–0.77)	43.2	Reference		Reference
Model 2†: Model 1 + cardiac CT	0.92 (0.91–0.94)	227.3	0.718 (0.589–0.813)	0.162 (0.102–0.245)	P<0.001
Model 3‡: Model 2 + LACI	0.95 (0.94–0.96)	290.1	0.768 (0.677–0.846)	0.210 (0.173–0.299)	P<0.001
Model 2 + LAV _i min	0.93 (0.92–0.94)	238.9	0.722 (0.580–0.780)	0.171 (0.111–0.253)	P<0.001
Model 2 + LVEDVi	0.92 (0.91–0.94)	231.5	0.723 (0.593–0.817)	0.166 (0.104–0.249)	P<0.001

IDI: integrative discrimination index; LAV_imin: left atrial end-diastolic volume indexed (minimum); LR: likelihood-ratio; LVEDVi: left ventricular end-diastolic volume indexed; NRI: net reclassification improvement.

* Covariables in the **model 1** (traditional risk factors): age, male, diabetes, hypertension, smoking, dyslipidemia.

† Covariables in the **model 2** (cardiac CT): model 1 + LVEF (per 5% increase in LVEF), Number of segments with stenosis > 70%, Number of segments with noncalcified plaques, and Number of vessels with obstructive CAD.

‡ Covariables in the **model 3** (LACI): model 2 with LACI value per 1%.

Human rights

The authors declare that the work described has been performed in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients. The authors declare that they obtained a written informed consent from the patients included in this article.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Ethical statement – declarations

Ethics approval and consent to participate: The study was approved by the local Ethic Committee of our Institutions and conducted in accordance with the 1964 Declaration of Helsinki. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. All patients enrolled in this study were required to understand and give their consent for participation and provided informed written consent.

Credit author statement

All authors participated in the discussion of the concept of the study.

Théo Pezel: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

Jean Guillaume Dillinger: Data curation; review & editing.

Solenn Toupin: Formal analysis; Methodology; Writing - review & editing.

Raphael Mirailles: Data curation; review & editing.

Damien Logeart: Data curation; review & editing.

Alain Cohen-Solal: Data curation; review & editing.

Alexandre Unger: Data curation; review & editing.

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Alexandre Boutigny: Data curation; review & editing.

Tania Ah-Sing: Data curation; review & editing.

Lounis Hamzi: Data curation; review & editing.

Joao A.C. Lima: Methodology; Writing - review & editing.

Valérie Bousson: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Software; Supervision; Writing - review & editing.

Patrick Henry: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; review & editing.

Declaration of Competing Interest

Solenn Toupin is employee of Siemens Healthcare. The other authors declare that they have no competing interests.

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Partie 9 :

Discussion générale des résultats

Les maladies cardiovasculaires restent un problème de santé publique majeur, ce qui s'accompagne de coûts directs et indirects extrêmement importants, évalués à plus de 169 milliards d'euros par an au sein de l'Union Européenne (85), et plus de 350 milliards de dollars par an aux États-Unis (3). Ainsi, il est absolument crucial de d'élaborer un outil de stratification pronostique précoce capable de détecter les patients les plus à risque de présenter ces évènements cardiovasculaires afin de leur offrir une prise en charge personnalisée.

Dans ce but, l'imagerie cardiaque multimodale représente un outil non invasif de choix. Alors que de nombreuses études ont montré l'intérêt pronostique de l'évaluation des paramètres structurels et fonctionnels du ventricule gauche (55,56,78,79) et de l'oreillette gauche séparément (80), aucune étude n'avait jusqu'alors mesuré l'intérêt d'évaluer simultanément le ventricule gauche et l'oreillette gauche. Ainsi, du fait de l'étroite relation physiologique qui existe entre l'oreillette et le ventricule gauches, rapportée par plusieurs études (81–83), l'hypothèse de ce travail de thèse de science était que l'évaluation du couplage auriculo-ventriculaire gauche pourrait permettre de refléter l'existence d'une dysfonction auriculo-ventriculaire précoce, et constituer alors un meilleur outil de prédiction précoce du risque d'évènement cardiovasculaire. Pour ce faire, nous avons développé le premier indice de couplage auriculo-ventriculaire gauche décrit dans la littérature (84). Ce travail de thèse a été réalisé en différentes étapes qui vont être résumées dans cette partie d'analyse globale des résultats.

Ainsi, l'étude n°1, (84) a permis à l'aide de la cohorte américaine MESA de développer l'indice de couplage auriculo-ventriculaire gauche (LACI) qui est défini simplement par le ratio du volume de l'oreillette gauche en télédiastole sur le volume du ventricule gauche en télédiastole. Cet indice exprime alors le pourcentage de dysfonction auriculo-ventriculaire gauche. Il est important de mentionner que cet indice a été initialement développé en utilisant les données d'IRM cardiaque, qui est l'examen d'imagerie cardiaque le plus robuste dans la mesure des volumes ventriculaires et auriculaires gauches dans la littérature (30,86,87). Cette utilisation de l'IRM cardiaque constitue une véritable force de ce travail afin de lui donner une robustesse scientifique importante pour ce travail de type preuve de concept qui vise à la création du premier indice de couplage auriculo-ventriculaire gauche décrit dans la littérature.

Dans ce premier travail, nous avons montré que la mesure uniquement du ventricule gauche ou uniquement de l'oreillette gauche n'est pas suffisante pour stratifier le risque d'évènement cardiovasculaire, et qu'un indice de couplage mesurant simultanément l'oreillette et le ventricule gauche permet de prédire avec une performance supérieure, le risque de survenue d'évènement cardiovasculaire comprenant l'insuffisance cardiaque, la fibrillation atriale, le décès de cause coronaire et les évènements cardiovasculaires graves en général. Ce travail de thèse a été initié par le doctorant lors de sa mobilité pendant deux ans au sein du *Johns Hopkins Hospital (Baltimore, USA)* sous la direction du Pr Joao Lima. Au cours de sa mobilité il a pu commencer ce travail sur la cohorte MESA qui est une étude multicentrique réalisée sur 6 centres américains avec un recrutement prospectif allant de 2000 à 2002, ayant permis de recruter 6 814 participants âgés de 45 à 84 ans, avec tous pour particularité le fait d'être indemne de maladie cardiovasculaire au moment de leur recrutement (88). Avec un suivi médian de plus de 15 ans aujourd'hui et la réalisation de nombreux examens d'imagerie cardiovasculaire à l'inclusion et dans le suivi, la cohorte MESA constitue l'une des cohortes

d'imagerie cardiovasculaire les plus impactantes au monde, afin de développer les outils de stratification pronostique de demain, en prévention primaire (89).

Dans cette étude n°1, nous avons montré que le LACI était indépendamment associé à la survenue des événements cardiovasculaires. Afin de pouvoir proposer une utilisation en routine de ce nouvel indice, nous avons déterminé son meilleur seuil de discrimination pronostique qui est de 25%. Ainsi, une valeur de LACI strictement supérieure à 25 % était associée de façon indépendante et après ajustement sur les facteurs de confusion potentiels, à la survenue de fibrillation atriale, d'insuffisance cardiaque, de mortalité de cause coronaire et d'évènements cardiovasculaires graves. Plus intéressant encore, nous avons montré dans ce travail que le LACI avait une valeur pronostique supérieure à n'importe quel paramètre mesuré de l'oreillette gauche et/ou du ventriculaire gauches évalués séparément (84). Ainsi, ce premier travail montre l'intérêt de l'évaluation du couplage auriculo-ventriculaire gauche en tant qu'indice pronostique en prévention primaire. Ces résultats constituent un premier signal fort en faveur de l'importance de l'évaluation de ce couplage auriculo-ventriculaire gauche, pour améliorer nos outils de prédiction en prévention primaire.

Après l'obtention de notre premier de couplage auriculo-ventriculaire gauche (LACI) et la confirmation de son intérêt pronostique, nous avons fait l'hypothèse d'utiliser cet indice comme un marqueur indirect de fonctionnement du couplage auriculo-ventriculaire gauche. Ainsi, en étudiant les paramètres déterminant la valeur du LACI, nous pouvons indirectement investiguer les déterminants impliqués dans le couplage auriculo-ventriculaire gauche et sa dysfonction. C'était l'objet de l'étude n°2 de cette thèse de science basée sur l'étude MESA (90). Cette étude a donc permis de mettre en évidence les déterminants du couplage auriculo-

ventriculaire gauche mais également de sa variation annuelle moyennée sur 10 ans, autrement dit de sa dégradation avec le temps. Tout d'abord, nous avons montré qu'une augmentation de l'âge était fortement associée à la dégradation du couplage auriculo-ventriculaire gauche et de la rapidité de sa dégradation, et cela même après ajustement pour tous les facteurs de confusion potentiels. Bien qu'il n'y ait pas de différence au moment de l'inclusion des patients entre hommes et femmes quant à l'évaluation de ce couplage auriculo-ventriculaire, la rapidité de dégradation de ce couplage auriculo-ventriculaire était franchement plus élevée chez les femmes que chez les hommes, et particulièrement après la ménopause. Concernant l'ethnicité des participants, notre étude a montré que les afro-américains avaient au moment de leur inclusion et après ajustement sur les facteurs de confusion potentiels une dysfonction du couplage auriculo-ventriculaire gauche plus importante que pour les autres patients. Cela est très intéressant car de nombreuses études ont montré que les afro-américains avaient un risque d'évènement cardiovasculaire multiplié par 2 à 3 comparé aux autres individus aux États-Unis. Ce phénomène persiste d'ailleurs après ajustement sur des facteurs sociaux, économiques et environnementaux faisant alors l'hypothèse de l'implication de phénomènes physiopathologiques propres par exemple la rigidité artérielle plus importante chez ces patients. Ainsi le LACI pourrait être un marqueur expliquant le fait que les afro-américains présentent un risque cardiovasculaire plus élevé. Il est par ailleurs très intéressant de noter que les patients diabétiques et obèses présentaient une dysfonction auriculo-ventriculaire gauche plus importante que les autres individus. Ces résultats avaient déjà été rapportés au niveau de l'oreillette gauche chez les patients obèses et diabétiques du fait d'un rôle métabolique important au niveau de l'oreillette gauche (7,77). Enfin, la force de ce travail translationnel a été de pouvoir évaluer un certain nombre de biomarqueurs cardiaques (NT-proBNP, troponine), de fibrose (Cartographie T1 et ECV en IRM cardiaque), et d'inflammation (IL-6, CRP, Fibrinogène). Ainsi, nous avons montré que cette dysfonction du couplage auriculo-

ventriculaire gauche était corrélée aux marqueurs de fibrose myocardique du ventricule gauche mesurés par IRM cardiaque. Le LACI était également corrélé avec la concentration de NT-proBNP ce qui est cohérent avec nos résultats qui soulignent qu'une dysfonction importante du couplage auriculo-ventriculaire gauche est associée à un risque d'insuffisance cardiaque plus important. Cependant, il n'y avait pas d'association entre le LACI et les biomarqueurs de l'inflammation.

Après avoir identifié les déterminants impliqués dans la dégradation du couplage auriculo-ventriculaire gauche en utilisant le LACI, nous avons constaté une différence significative dans l'évolution de la dégradation de ce couplage entre les hommes et les femmes (90). Ainsi, l'étude n°3 a permis de montrer que la ménopause jouait un rôle significatif dans l'accélération de la dégradation de ce couplage auriculo-ventriculaire gauche impliquant un rôle des hormones sexuelles (91). En effet dans cette étude n°3 nous avons montré que le LACI et sa variation annuelle moyennée étaient dépendants du statut ménopausique et de la prise d'un traitement hormonal substitutif. Plus intéressant encore, nous avons établi que cette dégradation du couplage auriculo-ventriculaire gauche était corrélée aux taux de testostérone totale plasmatique et inversement corrélée aux taux d'estradiol plasmatique chez les femmes en période de péri-ménopause. Il est essentiel de rappeler que dans la littérature, le rapport testostérone total sur estradiol est l'un des biomarqueurs pronostiques les plus puissants chez les femmes en péri-ménopause, pour prédire le risque cardiovasculaire (92,93). Alors que de précédentes études n'avaient pas établi de corrélation entre cet indice pronostique fort et les paramètres isolés du ventricule gauche ou de l'oreillette gauche (94), le résultat que nous mettons en avant suggère une implication majeure de ces hormones sexuelles (95) dans le fonctionnement du couplage auriculo-ventriculaire gauche en période de péri-ménopause.

Dans ce travail, nous avons également pu mettre en évidence que la valeur du LACI et de sa variation annuelle moyennée sur 10 ans étaient indépendamment associées à la survenue d'évènements cardiovasculaires, y compris en prenant en compte dans le modèle final, le statut ménopausique et la prise d'un traitement hormonal substitutif chez les patientes en péri-ménopause. Cette valeur pronostique du LACI était d'ailleurs homogène chez les femmes en pré-ménopause et post-ménopause (91). A notre connaissance, il s'agit du premier travail suggérant l'importance du couplage auriculo-ventriculaire gauche dans la stratification pronostique des femmes en période de péri-ménopause.

Après avoir montré la valeur pronostique incrémentale de notre indice de couplage auriculo-ventriculaire gauche le LACI, comme marqueur du risque cardiovasculaire, les études n° 4 et 5 ont permis d'évaluer la valeur pronostique de sa variation annuelle moyennée sur 10 ans. En effet, l'étude n°4 a permis de mettre en évidence que la variation annuelle du LACI était un puissant facteur pronostique de survenue du risque de fibrillation atriale en prévention primaire (96). Plus intéressant encore, cette variation annuelle du LACI était supérieure en termes de performance pronostique à la variation annuelle de n'importe quel paramètre évaluant l'oreillette gauche et/ou le ventriculaire gauche pris séparément.

Dans la continuité de ce travail, l'étude n° 5 a montré également la valeur pronostique incrémentale de la variation annuelle du LACI pour prédire le risque d'insuffisance cardiaque (97). De façon analogue à l'étude n°4, la variation annuelle du LACI donnait la meilleure performance de prédiction du risque de survenue d'insuffisance cardiaque, au-delà de la variation annuelle de n'importe quel autre biomarqueur, ou paramètre d'évaluation du ventriculaire gauche ou de l'oreillette gauche.

Ainsi, les résultats des études n°4 et 5 renforcent le message de l'importance du couplage auriculo-ventriculaire gauche en montrant que sa mesure à un instant donné, ainsi que sa variation annuelle sont toutes les deux des facteurs pronostiques indépendants supérieurs à tous les paramètres d'imagerie du ventriculaire gauche ou de l'oreillette gauche évalués jusqu'alors en routine clinique.

Dans le cadre de sa thèse de science, le doctorant a eu l'opportunité lors de son retour en France, de pouvoir continuer son travail de recherche sur le couplage auriculo-ventriculaire gauche et de le valider à partir de plusieurs cohortes de validation françaises. Ainsi dans l'étude n°6, le LACI a pu être validé sur une cohorte française de patients ayant tous passé une IRM cardiaque de stress (98). Alors que les précédents travaux n'avaient jusque-là montré d'intérêt du LACI que sur la cohorte MESA, patients en prévention primaire indemnes de maladies cardiovasculaires au moment de leur évaluation (84,90,91,96,97), cette étude n°6 est la première étude évaluant l'intérêt d'un couplage auriculo-ventriculaire gauche chez des patients avec une maladie cardiovasculaire constituée. En effet, ce travail a permis de comparer la valeur pronostique du LACI au sein d'une population sans maladie cardiovasculaire et, d'une population avec un infarctus défini par la présence d'un rehaussement tardif sous-endocardique ou transmural ou la présence d'une ischémie inductible traduisant une maladie coronaire significative en IRM cardiaque de stress. Il est très intéressant de noter que la valeur pronostique du LACI pour prédire le risque d'évènement cardiovasculaire (ici mortalité cardiovasculaire ou hospitalisation pour insuffisance cardiaque aigüe) était homogène chez les patients sans maladie cardiovasculaire et ceux avec une maladie cardiovasculaire constituée (98). C'est donc la première étude qui montre que le LACI pourrait avoir un intérêt au-delà de la prévention primaire, pour stratifier le risque d'évènement cardiovasculaire et guider la prise en charge des médecins au quotidien.

La deuxième particularité de l'étude n°6 est qu'elle permettait de montrer l'excellente faisabilité et la grande performance de la mesure complètement automatisée du LACI par intelligence artificielle. En effet, ce travail a été réalisé en collaboration avec des ingénieurs en data spécialisés dans le développement d'algorithmes de segmentation automatique par intelligence artificielle, rattachés au Centre de « Recherche et Développement en intelligence artificielle » de Siemens Healthineers, Princeton, USA.

Enfin, le fait que cette étude montre l'excellente valeur pronostique du LACI supérieure à n'importe quel paramètre de mesure du ventricule gauche ou de l'oreillette gauche, renforce la robustesse des résultats qui avaient été présentés sur la première cohorte américaine dans les études n°1 à 5 (84,90,91,96,97). Afin de permettre un développement encore plus rapide de l'utilisation de ce couplage auriculo-ventriculaire, la validation de l'excellente faisabilité et de la conservation de la valeur pronostique du LACI par un algorithme complètement automatisé par intelligence artificielle à partir des données en IRM cardiaque, permet d'assurer le développement et la diffusion de cet outil à travers le monde.

Enfin, après avoir réalisé six premiers travaux afin de développer et de valider le premier indice de couplage auriculo-ventriculaire le LACI, à l'aide de l'IRM cardiaque, le doctorant s'est intéressé au travers de l'étude n°7 à valider et à évaluer le LACI à l'aide d'un scanner cardiaque (99). En effet, la validation de cet indice sur un scanner cardiaque permettrait d'assurer un développement beaucoup plus large de cette mesure, à travers le monde, compte tenu du fait que le scanner soit largement plus accessible en routine que l'IRM cardiaque. Ce travail a été réalisé par le doctorant sur la cohorte monocentrique de l'hôpital Lariboisière (Assistance Publique des Hôpitaux de Paris, AP-HP) à Paris de tous les patients adressés pour un coroscanner. Cette étude a montré l'excellente faisabilité de la mesure du LACI à l'aide du coroscanner. De plus la valeur pronostique du LACI a été également confirmée à l'aide de

cette cohorte de patients adressés pour un coroscanner. En effet, cette étude réalisée sur 1 444 patients a montré que le LACI restait indépendamment associé au risque de mortalité cardiovasculaire, au-delà des facteurs pronostiques et des biomarqueurs traditionnels. De façon intéressante, lorsque nous avons cherché à évaluer le meilleur seuil pronostique d'évaluation du LACI, nous avons retrouvé une valeur de LACI supérieure à 25 % – identique au seuil établi sur les données d'IRM cardiaque lors de la création de l'indice (84) – offrant la meilleure discrimination et reclassification du modèle pour prédire le risque de mortalité cardiovasculaire. Cela renforce la robustesse de ce seuil nous permettant de le recommander en routine clinique pour l'utilisation de notre indice de couplage auriculo-ventriculaire gauche.

Conclusion

Au final, ce travail de thèse a permis de développer le premier indice de couplage auriculo-ventriculaire gauche comme marqueur pronostique de risque d'évènement cardiovasculaire. Le doctorant a d'abord développé et validé l'intérêt pronostique de ce couplage chez des patients en prévention primaire indemnes de maladie cardiovasculaire, puis chez des patients avec une maladie cardiovasculaire constituée. Ensuite, le doctorant a montré qu'au-delà de sa mesure à un instant donnée, la variation annuelle du LACI entre deux examens d'imagerie réalisés à 10 ans d'intervalle avait également une valeur pronostique indépendante forte du risque d'événements cardiovasculaires. Enfin, le fait que cet indice de couplage auriculo-ventriculaire et sa variation annuelle soient supérieurs en termes de prédiction du risque d'événements cardiovasculaires à n'importe quel biomarqueur connu, mesure du ventricule gauche ou de l'oreillette gauche pris séparément, est un véritable plaidoyer en faveur de l'intérêt de la mesure simultanée de l'oreillette gauche et du ventricule gauche à l'aide du LACI. La validation de cet indice proposée par le doctorant à l'aide des données de scanner assure la diffusion et le développement de ce nouvel outil à travers le monde en routine clinique afin qu'il puisse bénéficier au plus grand nombre de patients.

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