TABLE DES MATIERES

ABBREVIATIONS (dans l'ordre d'apparition)

AFIJI	Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention
DDCD	Duke Databank of Cardiovascular Disease
Apo B	Apolipoprotéine B
IDM	Infarctus du myocarde
LDL-C	Lipoprotéine de faible densité
PCSK9	Proprotéine convertase subtilisine/kexine de type 9
HF	Hypercholestérolémie familiale
CRP-us	Protéine C réactive ultrasensible
IL-6	Interleukine 6
ARIC	Atherosclerosis Risk in Communities Study Description
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain)
IL-1β	Interleukine-1-béta
ACC	American College of Cardiology
AHA	American Heart Association
ESC	European Society of Cardiology

I. PREAMBULE

1. Déroulement de la thèse de sciences et mobilité

Cette thèse de science intitulée *« Athérosclérose coronaire prématurée : facteurs de risque, pronostic, prévention et nouvelles approches mécanistiques »*, a été débutée en novembre 2018, sous la direction du Pr Johanne Silvain et la codirection du Pr Jean-Philippe Collet, au sein de l'unité INSERM UMRS166. L'objectif était de développer et mener des travaux de recherche sur l'athérosclérose coronaire prématurée, en exploitant en particulier les données de la cohorte AFIJI *(Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention)* et des registres nord-américains similaires.

Ainsi, la première année de ce doctorat (2018 – 2019) s'est effectuée en mobilité aux Etats-Unis à Durham en Caroline du Nord, au sein de l'Université de Duke, au Duke Clinical Research Institute, sous la direction du Pr Tracy Wang et du Pr Matthew Roe, et au Duke Molecular Physiology Institute dirigé par le Pr Svati Shah. Les travaux de recherche effectués pendant cette mobilité ont été soutenus par des bourses de recherche accordées par la Fédération Française de Cardiologie, l'Institut Servier, et Action Cœur.

Les objectifs spécifiques de cette mobilité étaient les suivants :

- Apprendre la méthodologie spécifique des mégabases de données ;
- Développer des projets de recherche translationnels sur la maladie coronaire prématurée en collaborant avec le Duke Molecular Physiology Institute et en exploitant les bases de données du Duke Clinical Research Institute ;
- Acquérir les connaissances nécessaires au développement des projets de recherche ;
- Développer des collaborations internationales sur la thématique de la maladie coronaire prématurée.

La deuxième et la troisième année de cette thèse de science se sont déroulées au sein de l'équipe 2 « Athérothrombose et Pharmacologie appliquée » de l'unité INSERM UMRS 1166. L'objectif était de développer des collaborations avec les unités de recherche de Sorbonne Université pour poursuivre des travaux translationnels impliquant l'étude de l'inflammation et du vieillissement vasculaire dans la maladie coronaire prématurée.

2. Registre AFIJI : Histoire & Contribution aux connaissances sur la maladie coronaire

Depuis 1996, sous la direction du Pr Gilles Montalescot et du Pr Jean-Philippe Collet, l'étude de cohorte prospective AFIJI inclut les patients atteints d'une maladie coronaire prématurée – définie par des lésions coronaires significatives symptomatiques avant l'âge de 45 ans. Cette étude de cohorte, initialement monocentrique puis multicentrique, comprend dans son protocole une hospitalisation de jour entre 1 et 2 mois après la découverte de la maladie coronaire, puis un suivi annuel. Lors de cette hospitalisation de jour, des données cliniques spécifiques aux jeunes patients telles que le niveau socio-économique, l'activité sportive, mais aussi la présence de pathologies auto-immunes et inflammatoires sont collectées. Ce registre comprend une banque de données d'imagerie avec les angiographies coronaires, les échographies et doppler des artères carotides et fémorales ainsi que les imageries aortiques en IRM. Des échantillons sanguins sont également prélevés et préservés pour chaque patient inclus, permettant ainsi d'effectuer des analyses en fonction des projets de recherche : étude de la fibrine, de la viscoélasticité du caillot, recherche de thrombophilie, étude de la réactivité plaquettaire, du métabolisme du cholestérol ou de l'inflammation.

L'étude AFIJI a permis des découvertes scientifiques majeures dans le domaine de la maladie coronaire. En 2006, l'équipe de l'INSERM UMRSS 1166 a collaboré avec Penn University dans un projet de recherche visant à analyser les propriétés morphologiques de la

fibrine chez des patients atteints d'une maladie coronaire prématurée (1). En comparaison avec des volontaires sains appariés sur l'âge et sur le sexe, les jeunes patients coronariens présentaient une augmentation significative de la concentration plasmatique de fibrinogène ainsi qu'une fibrine plus rigide, constituée de fibres plus nombreuses et plus courtes (figure 1) ; par ailleurs la fibrine des jeunes coronariens était lysée à une vitesse plus lente que celle des témoins. Il s'agissait d'une première étude physiopathologique visant à expliquer la survenue d'une thrombose coronaire prématurée. Ces travaux ont ensuite été poursuivis par l'étude de la rigidité du caillot et de la réponse à la fibrinolyse dans une étude cas témoins incluant également une étude génotypique du profil de la fibrinolyse(2).

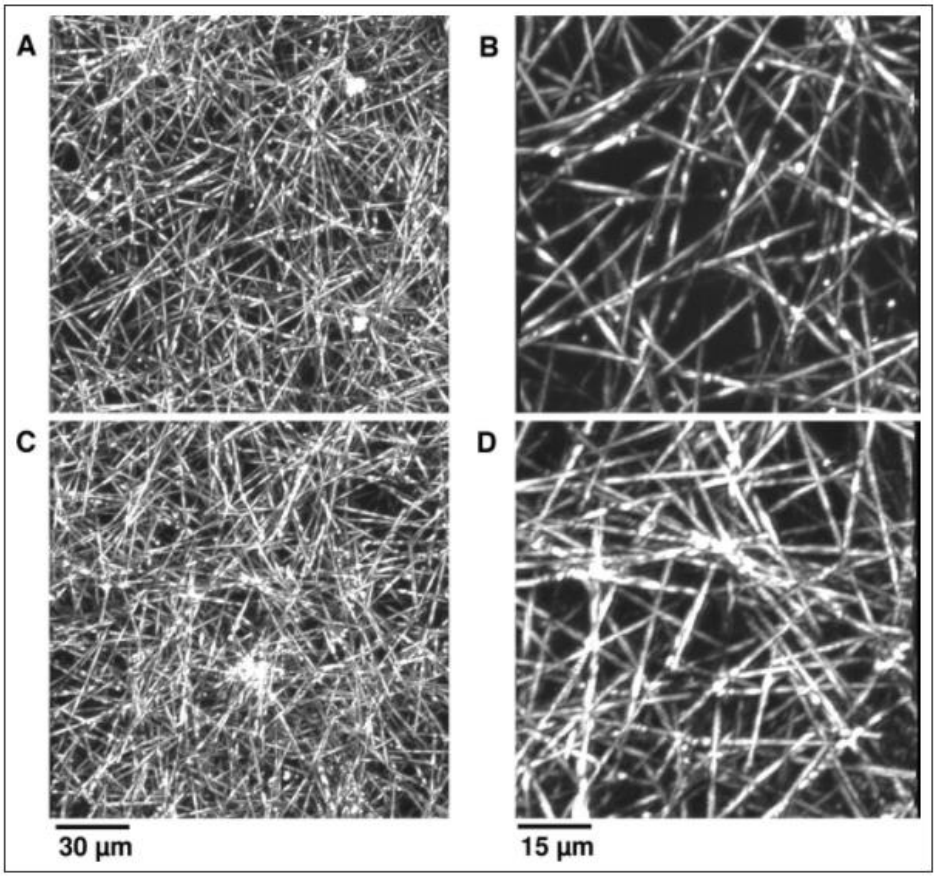

Figure 1. Images de reconstructions 2D de coupes optiques des matrices de fibrine issues de plasma de témoin sain et (A et B) et de patients AFIJI avec une maladie coronaire prématurée (C et D).

Ces images ont été obtenues par microscopie laser confocale à balayage faible (146 × 146 µm^2 pour A et C) et intermédiaire (73 × 73) µm2 pour les grossissements B et D). La concentration de fibrinogène était similaire dans cette paire appariée pour l'âge et le sexe (2,1 g/L).

Adapté de *Collet JP. al. Altered fibrin architecture is associated with hypofibrinolysis and premature coronary atherothrombosis. Arterioscler Thromb Vasc Biol 2006;26(11):2567–73.*

En 2009, l'exploitation du registre AFIJI a permis la publication d'une avancée majeure concernant la compréhension du mécanisme physiopathologique responsable des récidives ischémiques coronaires liées à des thromboses de stents des patients traités par une double anti-agrégation plaquettaire par aspirine et clopidogrel. L'analyse biologique et clinique de 259 jeunes patients du registre AFIJI ayant survécu à un premier infarctus du myocarde a permis de décrire le polymorphisme génétique responsable de la variabilité inter-individuelle de réponse au clopidogrel. En particulier, cette étude a mis en évidence l'association entre l'allèle CYP2C19*2 codant pour un cytochrome P450 non fonctionnel et la résistance au clopidogrel. Dans cette étude publiée dans la revue *The Lancet* en 2009, ce polymorphisme était responsable d'un risque de récidive ischémique ou de thrombose de stent multiplié par 3,5 **(figure 2)** (3). Cette première étude, issue du registre AFIJI, a entrainé une révolution dans le traitement des patients atteints d'un infarctus du myocarde en contribuant à la naissance des thérapies antiplaquettaires non dépendantes de ce polymorphisme génétique ou guidées par la génétique, qui font encore l'objet d'essais randomisés aujourd'hui (3, 4).

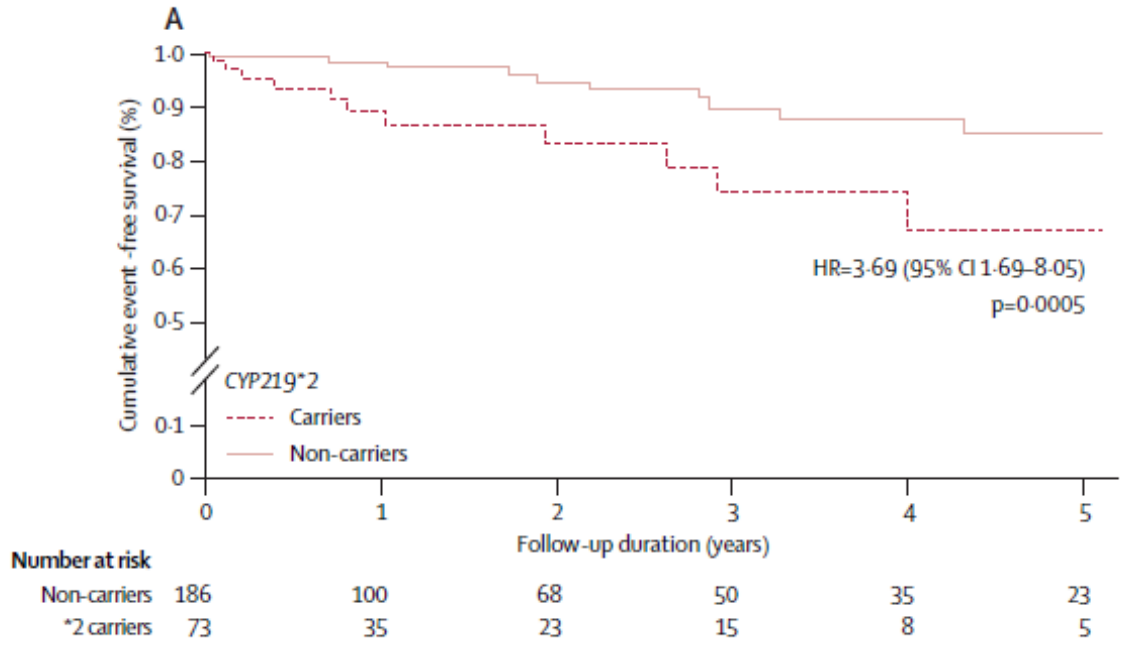

Figure 2. Analyse Kaplan-Meier des taux de décès, infarctus du myocarde ou revascularisation urgente pendant la période de suivi des patients porteurs d'une mutation CYP2C19*2 comparés aux non porteurs.

Adapté de *Collet J-P et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009;373(9660):309–17. Doi: 10.1016/S0140-6736(08)61845-0.*

3. Duke Databank of Cardiovascular Disease : Histoire & Contribution aux connaissances sur la maladie coronaire

La Duke Databank of Cardiovascular Disease (DDCD) est l'une des bases de données les plus larges et les plus anciennes de patients atteints de maladie coronaire et d'infarctus du myocarde. Cette base a été utilisée pour deux publications de cette thèse de science. Elle a été mise au point en 1967 sous l'impulsion du Dr Eugene Stead - président du département de médecine de Duke de 1946 à 1967 – grâce à une bourse de recherche de 5 ans accordée par le National Institute of Health, nommée *« Myocardial Infarction Research Unit ».*

Figure 3. Installation des unités centrales au niveau du laboratoire d'hémodynamique de Duke

L'objectif de cette bourse était de créer le premier registre informatique comprenant les données médicales des patients admis pour un infarctus du myocarde, grâce à une collaboration entre médecins, statisticiens, programmateurs et chercheurs. La vision futuriste des chefs de l'unité de cardiologie et du doyen établissait que l'informatique deviendrait un pilier important de la prise en charge des patients en soins intensifs ainsi que pour la recherche. Ainsi, une unité centrale informatique a été installée au sous-sol de l''unité de cardiologie aiguë **(figure 3 et 4)**.

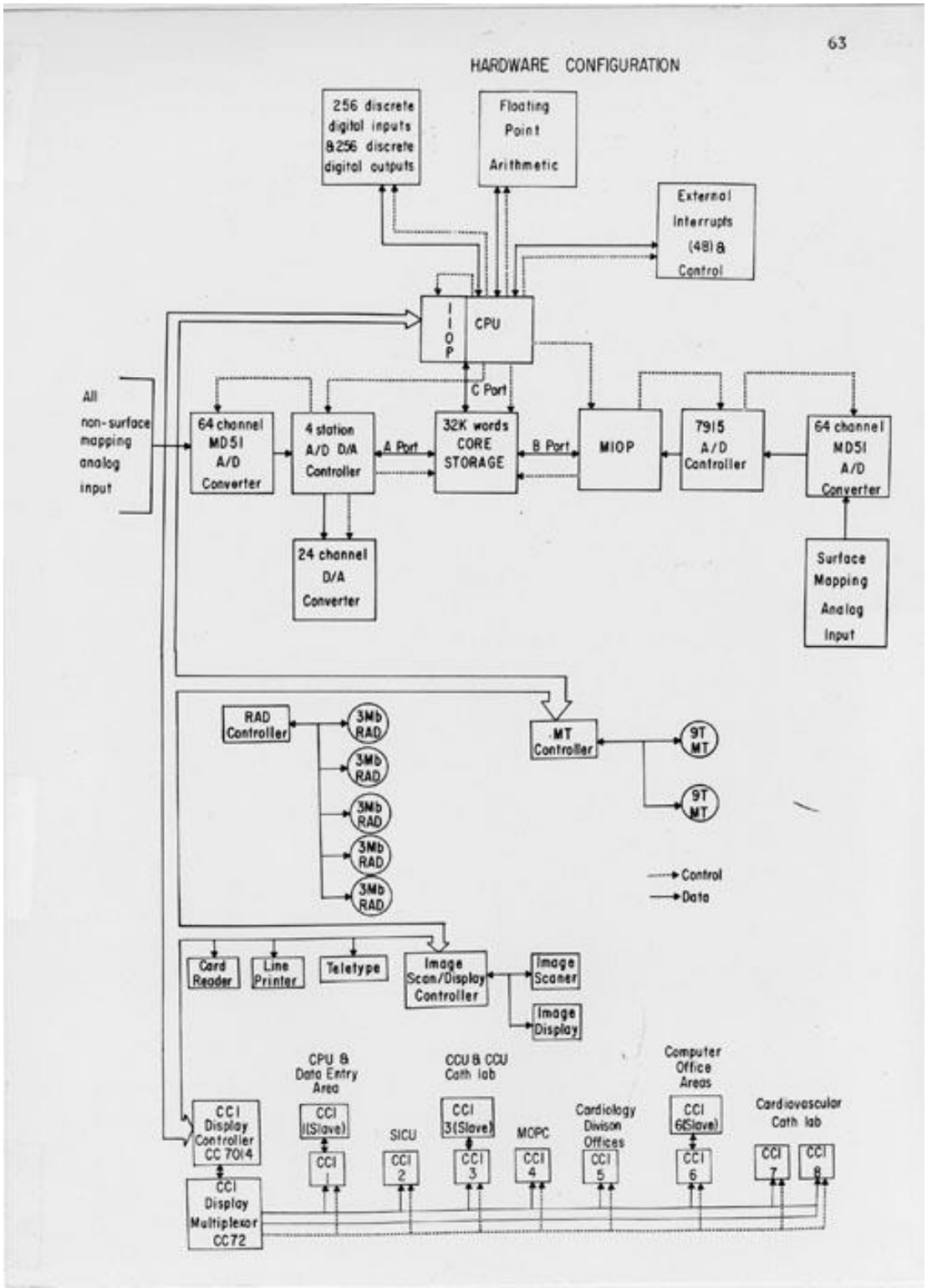

Figure 4. Configuration logistique et informatique de la *« Myocardial Infarction Research Unit »*

Ainsi, l'ordinateur est donc devenu une ressource pour le stockage et la récupération d'informations au sein du département de cardiologie, en recueillant au fil du temps des caractéristiques pré-spécifiées des patients admis en unité de soins continus et en laboratoire de cathétérisme cardiaque. La banque de données et ses modèles statistiques ont ainsi été utilisés pour des recherches susceptibles de modifier les principes fondamentaux de la pratique médicale. Ces progrès se sont concrétisés par la publication en 1970 des données hémodynamiques de 123 patients admis pour infarctus du myocarde (5). Les progrès réalisés ont permis d'accélérer le développement de la base de données avec l'ajout d'un laboratoire centralisé d'imagerie et d'électrocardiogramme en 1983. L'expérience du maniement de données multimodales d'une mégabase permettra de débuter les premiers essais cliniques du Duke Clinical Research Institute. Ainsi, en 1989, le méga-essai clinique randomisé GUSTO-1 inclura 41,021 patients atteints d'un infarctus du myocarde, randomisés entre différentes stratégies de fibrinolyse (6). En 2000, sous l'impulsion du Pr Svati Shah et du Pr Chris Granger, un sous-registre biologique nommé CATHeterization GENetics (CATHGEN) a été constitué au sein de la DDCD. Entre 2001 et 2010, les échantillons biologiques de 9334 personnes traitées au cours d'une coronarographie ont été recueillis, stockés et reliés aux données de la DCDD. Ces échantillons ont été recueillis afin de pouvoir générer des données moléculaires, cardiométabolique et génétiques (7). Ils ont également servi à deux travaux présentés dans cette thèse en collaboration avec le Duke Molecular Physiology Institute.

II. INTRODUCTION

1. Athérosclérose coronaire ou thrombose coronaire prématurée ?

L'athérosclérose est une maladie systémique complexe affectant les moyennes et grandes artères, y compris les artères coronaires. Au cours des dernières décennies, la compréhension de l'athérosclérose est passée de la considération d'un simple processus d'accumulation passive de lipides dans l'endothélium à la description d'une interaction entre inflammation locale et systémique, dysfonction endothéliale et accumulation active de lipides (8). Une plaque d'athérosclérose est une structure complexe composée de tissu conjonctif, de calcium, de cellules inflammatoires et de lipides dans des proportions différentes d'une plaque à l'autre. La consistance des plaques dépend de la proportion de leurs éléments constitutifs : une plaque fortement fibreuse et calcifiée est dure, alors qu'une plaque composée majoritairement d'esters de cholestérol et de macrophages contenant des lipides est molle. Une rupture ou une fissure de plaque permet au sang de pénétrer dans la plaque en favorisant ainsi la thrombose dans la lumière de l'artère, suivie d'une fragmentation et d'une embolisation.

La relation entre la thrombose et l'athérosclérose est complexe ; le modèle le plus souvent explicatif est la rupture de la plaque et l'érosion superficielle provoquant la formation d'un thrombus localisé, potentiellement occlusif. Le déclenchement du système de coagulation via le facteur XIIa, le facteur VIIa, le facteur tissulaire et finalement la thrombine joue un rôle central dans la médiation de l'athéro-thrombose. La perturbation de la surface endothéliale conduit également à l'adhésion plaquettaire, principalement par la liaison des récepteurs plaquettaires au collagène exposé et au facteur von Willebrand de la matrice sous-endothéliale exposée. De plus, les plaquettes sont activées via la voie de la coagulation et la thrombine (9, 10).

La survenue d'une thrombose coronaire chez un patient jeune a initialement questionné la relation athérosclérose – thrombose ; en effet, les premières descriptions angiographiques du début des années 1990 rapportent la présence d'un « thrombus dans des coronaires lisses, ou

avec seulement de l'athérosclérose ». Dans l'une des premières séries descriptives angiographiques de 504 jeunes patients admis pour un infarctus du myocarde, Zimmerman et al. ont observé que jusqu'à 30 % de ces individus avaient des coronaires normales, avec des plaques non obstructives (11). Par ailleurs, la majorité de ces patients présentait une atteinte coronaire modérée, mono tronculaire dans 60 à 80 % des cas (11–13). L'absence de suivi fiable et à long terme de ces patients – clinique ou angiographique – a contribué à renforcer l'hypothèse d'accidents thrombotiques ponctuels sans athérosclérose évolutive, avec un pronostic semblant correct dans la mesure où ils sortaient vivants de l'hôpital et se portaient mieux que leurs aînés durant les quelques mois de suivi décrits par les rares études de registres (11–13). Cette hypothèse a été remise en cause au début des années 2000 par les études physiopathologiques et d'imagerie intra-coronaire, avec l'émergence de deux concepts permettant de mieux comprendre la thrombose résultant d'une athérosclérose minime chez un jeune patient :

- l'importance des facteurs inflammatoires et du stress mécanique comme facteur de rupture de petites plaques et de thrombose (14).

- la capacité d'une rupture de plaque à déclencher une thrombose à distance, dans l'ensemble de l'arbre coronaire (15).

2. Premières hypothèses physiopathologiques sur la maladie coronaire prématurée

L'infarctus du myocarde chez un individu d'âge jeune a longtemps été considéré comme un accident de parcours secondaire à une pathologie sous-jacente, ou encore plus simplement une forme identique mais précoce d'une maladie qui est normalement celle du sujet âgé. Comme décrit précédemment, l'hypothèse physiopathologique longtemps défendue et recherchée en pratique clinique était celle de la présence d'anomalies de l'hémostase, entrainant une thrombophilie. Comme expliqué précédemment, cette hypothèse reposait sur les observations angiographiques initiales des coronaires des jeunes patients atteints d'un infarctus du myocarde, décrivant un « thrombus dans des coronaires normales ou peu athéromateuses » (11, 16).

Au début des années 1980, l'imputabilité des troubles de l'hémostase dans la survenue d'accidents thrombotiques veineux est bien établie avec la découverte des déficits en protéine C et protéine S (17, 18). Au début des années 1990, l'avancement dans les techniques de séquençage et la multiplication des études cas-témoins permettent de démontrer que des mutations dans les gènes codant pour des protéines impliquées dans la formation de thrombus jouent un rôle important dans la prédisposition à un état d'hypercoagulabilité persistant et spontané (19, 20). Parmi ces avancées, la plus connue est probablement la découverte de l'implication de la mutation du facteur V de Leiden dans la résistance à la protéine C (21–23). De manière concomitante, une équipe de chercheurs danois met en évidence au début des années 2000 la mutation en position 20210 du gène codant pour la prothrombine, présente chez 2% de la population danoise, et associée à un risque de thrombose veineuse multiplié par 3 (24). Par ailleurs, de nouvelles anomalies héréditaires potentiellement associées aux thromboses vasculaires ont été décrites : anomalies du facteur VII et du fibrinogène, homocystéinémie et polymorphisme de la glycoprotéine GPIIIa (25–27).

Bien que la plupart de ces variations génétiques aient été décrites comme facteurs de risque de thrombose veineuse, la question de leur imputabilité dans la thrombose artérielle s'est posée, notamment chez les jeunes patients avec un infarctus du myocarde (21). Sur la base de l'observation de « thrombus dans des coronaires saines chez les jeunes patients», l'hypothèse d'une association entre thrombophilie et thrombose coronaire prématurée a rapidement émergé (28–33). Parmi les études les plus exhaustives, on peut citer la méta-analyse de la Copenhague City Heart Study et 2 autres études de cohorte prospectives, totalisant plus de 21 ans de suivi, ne retrouvant pas de contribution des mutations du facteur V de Leiden aux évènements ischémiques artériels, quel que soit leur âge d'apparition (30). La grande majorité de ces études (**tableau 1)** n'a mis en évidence d'association entre thrombophilie et évènements cardiovasculaires précoces, hormis pour la mutation homozygote de la prothrombine pour laquelle les résultats sont discordants en fonction des cohortes.

Ainsi, l'hypothèse d'une thrombophilie est rapidement apparue comme une explication insuffisante pour expliquer la thrombose coronaire aiguë chez les patients jeunes. De même, le développement du coroscanner, de la détection des plaques à haut risque et de l'imagerie intra-coronaire non invasive et invasive, a progressivement éloigné l'hypothèse de « thrombus dans des coronaires saines ». Enfin, les premières observations que nous avions faites sur la base des données AFIJI et de notre pratique clinique laissaient entrevoir une hypothèse toute autre : celle selon laquelle la majorité des thromboses observées sont le fruit d'une athérosclérose coronaire prématurée évolutive, chronique et systémique (34).

Tableau 1 : Principales études sur les associations entre thrombophilie et infarctus du myocarde

Reference	Année	Nombre de patients	Anomalie hémostase testée	Association
Corral et al. (28)	1997	101 patients avec IDM 101 individus sains	Mutation gène G20210A Mutation Facteur V Leiden	**oui** non
Boekholdt et al. (29)	2001	1302 patients avec IDM 2093 individus sains	Mutation Facteur V Leiden Mutation de l'inhibiteur de l'activateur du plasminogène 1 Mutation fibrinogène G 455A Mutation gène G20210A	non non non non
Juul et al. (30)	2002	469 patients avec IDM 7907 individus sains	Mutation Facteur V Leiden	non
Thrombosis and Vascular Biology Italian Study Group (31)	2003	210 patients avec IDM avant 45 ans 1210 individus sains	Mutation fibrinogène G 455A Mutation Facteur V Leiden Mutation gène G20210A Mutation G10976A du factor VII Mutation C807T glycoprotéine plaquettaire Ia Mutation C1565T glycoprotéine plaquettaire IIIa Mutation G185T facteur XIII Mutation de l'inhibiteur de l'activateur du plasminogène 1	non non non non non non non non
Rallidis et al. (32)	2003	70 patients avec IDM à 36 ans 260 individus sains	Mutation gène G20210A Mutation Facteur V Leiden Déficit protéine C Déficit protéine S Déficit en antithrombine III	**oui** non non non non
Rallidis et al. (33)	2017	255 patients avec IDM avant 36 ans 400 individus sains	Mutation gène G20210A Mutation Facteur V Leiden Déficit protéine C Déficit protéine S Déficit en antithrombine III Syndrome des antiphospholipdes	**oui** non non non non non

IDM pour Infarctus du Myocarde

3. Place de l'hypercholestérolémie familiale hétérozygote

L'hypercholestérolémie familiale est la maladie monogénique la plus courante et la plus grave du métabolisme des lipides (35). Il s'agit d'une maladie héréditaire autosomique dominante causée principalement par des mutations du gène codant pour le récepteur du LDL-C (lipoprotéine de faible densité), du gène de l'apoliprotéine B (Apo B) et du gène codant pour l'enzyme PCSK9 (Proprotéine convertase subtilisine/kexine de type 9). Les mutations du récepteur du LDL-C sont les plus fréquentes et représentent 85 à 90% des cas d'hypercholestérolémie familiale : elles entrainent une perte de fonction du récepteur LDL-C et donc une baisse de la clairance du cholestérol. Les mutations de l'ApoB - responsables de la réabsorption défectueuse du LDL-C plasmatique - et la mutation PCSK9 - responsable d'une dégradation accélérée du récepteur LDL-C - sont plus rares et sont respectivement retrouvées dans 10% et 5% des cas (36). Tandis que les formes homozygotes présentent des stigmates cliniques précoces dès la naissance et un pronostic sombre, la forme hétérozygote évolue silencieusement, provoquant une athérosclérose prématurée. Malgré une association significative avec la survenue d'athérosclérose prématurée (37, 38), l'hypercholestérolémie familiale hétérozygote est une pathologie complexe à dépister, nécessitant des équipes expertes et l'utilisation de scores de risque impliquant des critères cliniques, paracliniques et génétiques.

Le Dutch Lipid Clinical Network est le score de dépistage d'hypercholestérolémie familiale hétérozygote le plus utilisé (39–41) : ce score, qui est présenté dans le **tableau 2**, classe les patients entre hypercholestérolémie familiale (HF) peu probable (0 - 2), HF possible (3 - 5), HF probable (6 – 8) et HF certaine (> 8). Selon les études de registre, l'hypercholestérolémie familiale toucherait entre 0,4 et 0,5% de la population générale, soit 1 adulte sur 250 (42, 43). Étant donné que ces études sont principalement fondées sur des critères cliniques et biologiques – avec des tests génétiques rarement effectués - la prévalence réelle de l'HF certaine/probable pourrait être sous-estimée (44).

Tableau 2 : Critères du Dutch Lipid Clinical Network

Critères	Points
Antécédent personnel	
Maladie coronaire prématurée	2
Antécédents familiaux	
Parent du 1er degré avec une maladie coronaire ou vasculaire prématurée (homme <55 ans ; femme <65)	1
Parent du 1er degré avec xanthomes tendineux ou arc cornéen précoce ou enfants < 18 ans avec LDL-cholestérol ≥95e percentile selon l'âge, le sexe et l'ethnie	2
Examen physique	
Xanthomes tendineux	6
Arc cornéen précoce < 45 ans	4
LDL-C avant traitement	
LDL ≥ 330 mg/dL	8
LDL 250-329 mg/dL	5
LDL 190-249 mg/dL	3
LDL 155-189 mg/dL	1
Test génétique	
Mutation LDLR, apoB or PCSK9	8
Diagnostic	
Hypercholestérolémie Familiale certaine	>8
Hypercholestérolémie Familiale probable	6-8
Hypercholestérolémie Familiale possible	3-5
Hypercholestérolémie Familiale peu probable	<3

La recherche d'une hypercholestérolémie familiale chez les patients atteints d'une maladie coronaire a donné des résultats variables en fonction des populations étudiées et des critères diagnostiques impliqués **(tableau 3)**. Dans une analyse de l'enquête de *Action européenne sur la prévention secondaire et primaire par l'intervention pour réduire les événements*, qui a inclus 7000 patients hospitalisés pour un syndrome coronarien aigu ou une procédure de revascularisation, la prévalence de l'hypercholestérolémie familiale a été estimée à 8,3%, et 15,4% dans le sous-groupe des 2212 patients âgés de moins de 60 ans (45).

D'autres études de taille plus petite ont également estimé la prévalence de l'hypercholestérolémie familiale chez les patients atteints d'infarctus du myocarde dans différentes régions géographiques : dans le golfe arabique, une étude de cohorte de 3224 patients a rapporté une incidence de 3,7% de l'hypercholestérolémie familiale chez des patients admis en unité de soins intensifs de cardiologie pour un infarctus du myocarde (44). En Australie, l'équipe de Pang et al. a démontré une prévalence de 14,3% chez 175 patients âgés de moins de 60 ans admis pour infarctus du myocarde (47). Dans notre sous-étude génétique de la DCDD (n=632 patients), moins de 1% des patients admis avec une maladie coronaire prématurée avant l'âge de 55 ans avaient une mutation responsable d'hypercholestérolémie familiale, tous impliquant le gène codant pour LDL-R.

Tableau 3 : Prévalence de l'hypercholestérolémie familiale

Référence	N	Population	Age moyen	Critère	Prévalence
Population générale					
de Ferranti (42)	36949	Population américaine	46.8	Dutch Lipid Clinic	0.40%
Bucholz (43)	42471	Population américaine	NA	Dutch Lipid Clinic	0.47%
Benn (39)	69016	Population danoise	58	Dutch Lipid Clinic	0.73%
Patients avec SCA					
Amor-Salamanca (48)	103	SCA ≤ 65	54	Genetique et Dutch Lipid Clinic	8.7% / 27.1%
Al-Rasadi (46)	3224	SCA	60	Dutch Lipid Clinic	3.70%
Nanchen (49)	4778	SCA	64.8	Dutch Lipid Clinic	1.60%
De Backer (45)	7044	SCA	64.8	Dutch Lipid Clinic	8.30%
Maladie coronaire prématurée					
Pang (47)	175	SCA	<60	Dutch Lipid Clinic	14.30%
Nanchen (49)	1451	SCA	≤55 M, ≤60 F	Dutch Lipid Clinic	4.80%
De Backer (45)	2212	SCA	<60	Dutch Lipid Clinic	15.40%
Singh (50)	1996	SCA	<50	Dutch Lipid Clinic	9%
Zeitouni (51)	632	SCA et angor stable	< 50	Génétique	0.6%

4. Contribution de l’inflammation

In vivo, l'inflammation participe à toutes les étapes de la genèse de l’athérosclérose et de la thrombose, en provoquant un dysfonctionnement endothélial, en favorisant la rupture de la plaque d’athérome et en participant à la formation du thrombus (52). Dès le milieu des années 1990, les études épidémiologiques ont indiqué que l'inflammation - mesurée soit par protéine C réactive ultrasensible (CRP-us) soit par l'interleukine-6 (IL-6) - était significativement associée à de futurs événements vasculaires en prévention primaire et secondaire, alors même que les facteurs de risques cardiovasculaire classiques tels que le tabac, le cholestérol, le diabète ou la pression artérielle étaient contrôlés (53–55). La mesure de l’inflammation s’est ainsi révélée être un outil efficace et pertinent pour mesurer le risque cardiovasculaire, intégrant le panel de ce qui est dorénavant appelé le risque cardiovasculaire résiduel.

En prévention primaire, l'évaluation du biomarqueur inflammatoire CRP-us ajoute des informations pronostiques à des mesures conventionnelles de risque cardiovasculaire avec une amplitude d'effet comparable à celui du LDL-cholestérol. Ainsi, les dernières recommandations internationales américaines et européennes préconisent l'utilisation de la CRP-us comme « marqueur de risque » impliqué dans la décision de déclencher des thérapeutiques par statines et une surveillance cardiovasculaire (56, 57). Ces recommandations sont fondées en grande partie sur les données de l'essai JUPITER publié en 2008 (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) dans lequel la rosuvastatine réduisait la survenue du premier infarctus du myocarde, d’accident vasculaire cérébral ou de décès cardiovasculaire de 40 % lorsqu'elle est administrée à des patients présentant un LDL-cholestérol bas mais une CRP élevée (54).

L’hypothèse d’une contribution forte de l’inflammation dans la survenue d’une athérosclérose coronaire et des phénomènes de thromboses prématurées s’appuie également sur

les observations effectuées chez les jeunes individus atteints de pathologie inflammatoire et auto-immune chronique, en particulier les maladies inflammatoires chroniques intestinales, la polyarthrite rhumatoïde, la spondylarthrite ankylosante ou le rhumatisme psoriasique (58, 59). Il a été observé chez ces patients, de manière constante, une augmentation du risque relatif d'infarctus du myocarde prématuré, souvent de manière proportionnelle aux périodes inflammatoires de ces pathologies chroniques et au contrôle général de la pathologie (60). Ainsi, l'inflammation chronique et infraclinique comme contributeur majeur de maladie coronaire prématurée et de mauvais pronostic est une hypothèse exploitée dans les études qui seront présentées dans cette thèse.

5. Définitions de la maladie coronaire prématurée en Europe et aux Etats-Unis

Il n'existe actuellement pas de définition standard et universelle de l'âge définissant la maladie coronaire prématurée. Les principaux registres existants et leurs critères respectifs sont décrits dans le **tableau 4.** En France et dans plusieurs pays européens, la limite d'âge retenue pour définir la maladie coronaire prématurée est actuellement la survenue d'une maladie coronaire athérothrombotique à un âge inférieur à 45 ans (1, 61, 62). C'est notamment le cas du registre AFIJI, dans lequel la maladie coronaire prématurée est décrite comme étant *« une maladie coronaire obstructive d'origine athérothrombotique survenant avant l'âge de 45 ans »*. Les grands registres nationaux Suédois RIKS-HIA (Register of Information and Knowledge About Swedish Heart Intensive Care Admissions) et SCAAR (Swedish Coronary Angiography and Angioplasty Registry) ont également utilisé la limite de 45 ans lors de leur analyse des admissions et du pronostic intra-hospitalier de 4018 hommes et 1070 femmes admis pour un infarctus du myocarde prématuré (61). De manière similaire, *The Italian Genetic Study on Early-onset Myocardial,* parue en 2019, a inclus 2000 patients âgés de moins de 45 ans avec un infarctus du myocarde de type 1 pour étudier leur pronostic (62). Cette étude présente par ailleurs une durée de suivi médian remarquable de presque 20 ans, les inclusions ayant débuté dès 1980.

Sur la base des recommandations de leurs sociétés scientifiques sur la prévention et le dépistage des maladies cardiovasculaires, les chercheurs et cardiologues américains ont plutôt utilisé le seuil de 50 voire 55 ans (63–65). Le registre YOUNG-MI (n=1685 patients) est le principal registre américain qui s'est intéressé à la maladie coronaire prématurée, avec des investigateurs ayant choisi la limite de 50 ans. Ce registre rétrospectif extrait les codages et notes médicales du Research Patient Data Registry (RPDR) de Partners HealthCare impliquant plusieurs hôpitaux dont le Brigham & Women's Hospital et le Massachusetts General Hospital de Boston et a permis une description clinique plus approfondie des patients atteints d'un infarctus à un âge jeune. Contrairement aux registres cités plus haut, il ne comprend pas de données angiographiques précises.

En 2019, l'extraction effectuée de la base de la DDCD des patients atteints d'une maladie coronaire prématurée – définie par une athérosclérose obstructive avant 50 ans - a permis de mettre au point la plus grande base américaine sur la maladie coronaire prématurée, constituée de plus de 5000 patients atteints d'un premier infarctus du myocarde avec des données cliniques, angiographiques et de suivi exhaustif.

Tableau 4 : Définitions de la maladie coronaire prématurée dans les différents registres dédiés

	Etudes Européennes			**Etudes Américaines**	
Registre	**AFIJI**	**The Italian Genetic Study on Early-onset Myocardial**	**RIKS-HIA et SCAAR**	**Young-MI**	**Duke Databank for Cardiovascular Disease**
Age	≤ 45 ans	≤ 45 ans	< 46 ans	< 50 ans	< 50 ans
Définition	Maladie coronaire obstructive	IDM type 1	IDM type 1	Maladie coronaire obstructive	Maladie coronaire obstructive
Type d'étude	Cohorte prospective	Cohorte prospective	Rétrospective	Prospective	Prospective
Nombre de patients	1200	2000	5088	1685	3655
Suivi médian	10 ans	19 ans	5 ans	11.2 ans	10 ans

6. Incidence de la maladie coronaire prématurée

Les principales données sur l'incidence de la maladie coronaire proviennent des registres américains tels que le National Cardiovascular Database Registry, et des études de cohorte s'intéressant à des communautés d'individus sur le long terme telles que la cohorte Atherosclerosis Risk in Communities Study Description (ARIC) ou les données collectées via les database hospitalières ou d'assurance (Health Partners, Blue Cross). Ces études précisent l'incidence globale de la maladie coronaire prématurée dans le temps ainsi que la proportion qu'occupent les jeunes patients dans la population des coronariens. Ces données varient en fonction des régions concernées, des dispositions socio-économiques et de l'accès au soin.

Aux Etats-Unis, Gupta et al. ont analysé la database de *Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project* (HCUP), l'une des principales assurances privées du pays. Le nombre absolu d'admissions pour infarctus du myocarde chez les femmes de moins de 55 ans était en augmentation de 56 à 61 pour 100 000 entre 2001 et 2010. En contraste, le nombre absolu d'admissions entre 2001 et 2010 chez les jeunes hommes est passé de 174 à 171 pour 100 000 (63). L'augmentation de l'incidence des jeunes patients admis pour un infarctus du myocarde, en particulier les jeunes femmes, a également été mis en évidence par le registre ARIC(64). Cette étude de cohorte prospective implique 4000 adultes de 45 à 64 ans de quatre communautés américaines (comté de Forsyth, Caroline du Nord, Jackson, Mississippi, banlieues de Minneapolis, Minnesota et comté de Washington, Maryland). L'objectif est d'étudier l'incidence de l'athérosclérose et ses conséquences ainsi que la variation des facteurs de risque cardiovasculaire, des soins médicaux et de la maladie selon le sexe, le lieu et le temps. Chaque adulte inclus dans l'étude ARIC est examiné deux fois, à trois ans d'intervalle, avec l'appui de centres de coordination, d'échographie, de pneumologie, d'électrocardiographie et de trois laboratoires centraux. Les examens complémentaires comprennent une échographie des artères carotides et poplitées, un bilan des lipides, lipoprotéines et apolipoprotéines (66). Ainsi,

l'analyse du registre ARIC a démontré une augmentation significative du nombre de patients admis pour un infarctus du myocarde avant l'âge de 55 ans entre 1995 à 2014, résultant surtout de l'augmentation des admissions pour infarctus du myocarde chez les jeunes femmes, alors que la proportion d'hospitalisations des jeunes hommes est restée assez stable **(figure 5)**. Cette tendance est parallèle à une augmentation de l'incidence des facteurs de risques cardiovasculaire, notamment l'hypertension et le diabète de type 2.

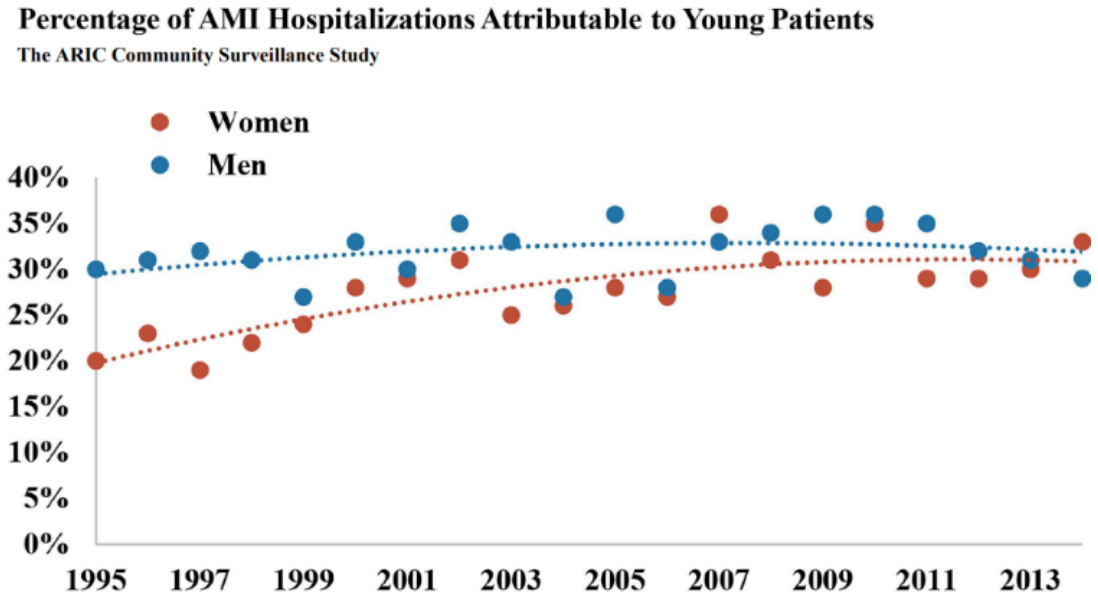

Figure 5. Incidence des admissions pour infarctus du myocarde des individus de moins de 55 ans dans le registre ARIC.

Adapté de *Arora Sameer et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized with Acute Myocardial Infarction: The ARIC Community Surveillance Study. Circulation, 2018*

L'analyse de la base de données angiographique du centre de cardiologie de la Pitié-Salpêtrière a également démontré une augmentation de la proportion des infarctus prématurés (<45 ans), atteignant une proportion de 10 % ces dernières années **(figure 6)**.

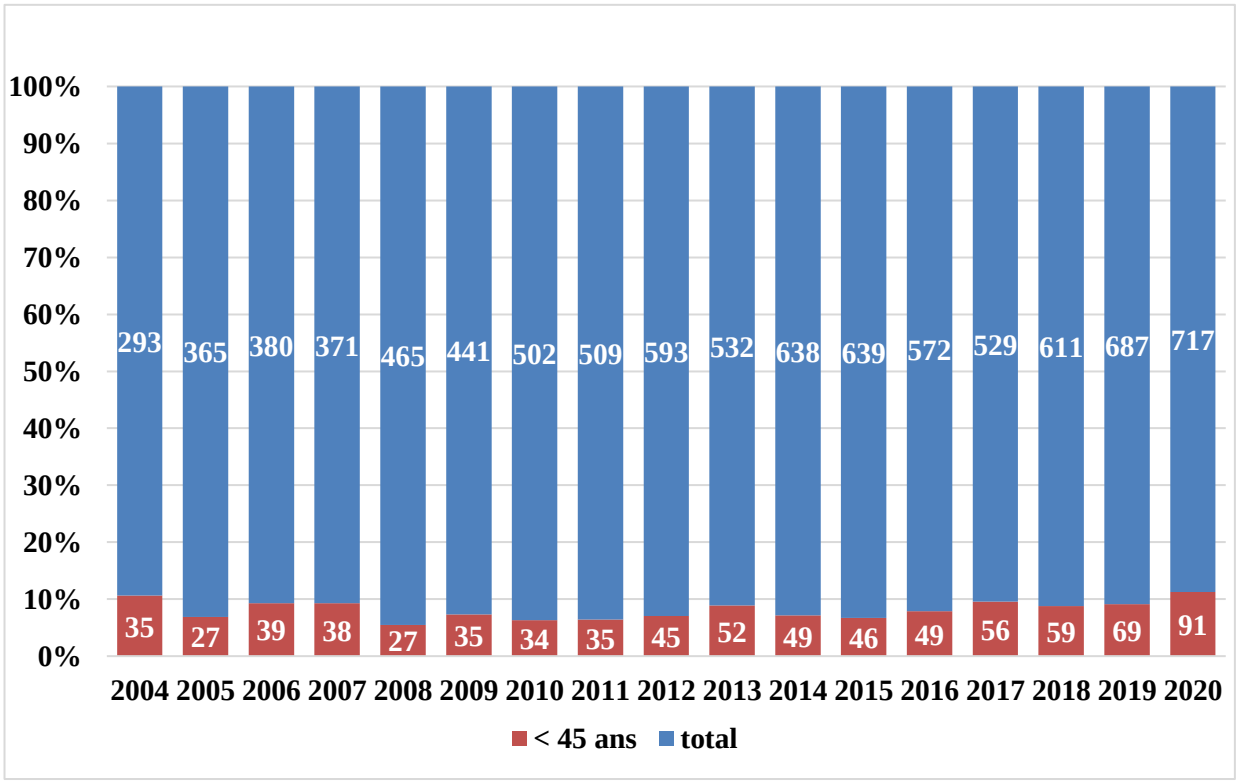

Figure 6. Nombre de syndromes coronariens aigus par année à la Pitié Salpêtrière comprenant les individus de 45 ans ou moins

III. JUSTIFICATION SCIENTIFIQUE DE LA THESE

Il n'existe actuellement que des données très limitées sur la physiopathologie et le pronostic de la maladie coronaire prématurée. La quasi-totalité des connaissances actuelles sur l'athérosclérose coronaire prématurée et l'infarctus du myocarde du sujet jeune sont des extrapolations des données issues d'essais randomisés et d'étude de registres impliquant une population de patients coronariens ayant un âge « moyen », c'est-à-dire âgée de 60 à 70 ans en Europe et en Amérique du Nord (67, 68) **(figure 7)**. Pour note, la moyenne d'âge des patients inclus dans les études randomisées de référence évaluant les inhibiteurs puissants du récepteur $P2Y_{12}$ plaquettaire dans le syndrome coronarien aigu était de 60 ans dans TIMI-TRITON-38 et de 59 ans dans l'étude PLATO (69, 70). De même, il n'existe que peu de données sur l'intérêt des nouveaux hypolipémiants inhibant le récepteur du PCSK9 dans une population de jeunes coronariens, alors qu'ils possèdent un potentiel intérêt chez les individus jeunes à haut risque cardiovasculaire et chez ceux ayant une maladie coronaire prématurée avérée dont le potentiel d'évolution est bien plus long que la moyenne des patients coronariens (71, 72).

Alors que la maladie coronaire prématurée concerne un segment de la population active, avec une espérance de vie théorique de 30 ans, il n'existe quasiment aucune donnée scientifique sur la physiopathologie, le pronostic et l'efficacité des traitements chez ces individus. Ce n'est que récemment, avec le développement des études de registres, des banques biologiques et plus généralement de la médecine personnalisée, que la question des patients à risque de développer de l'athérosclérose coronaire prématurée a fait surface dans des recommandations internationales qui n'ont pour le moment que peu de références scientifiques sur lesquelles s'appuyer (56, 57).

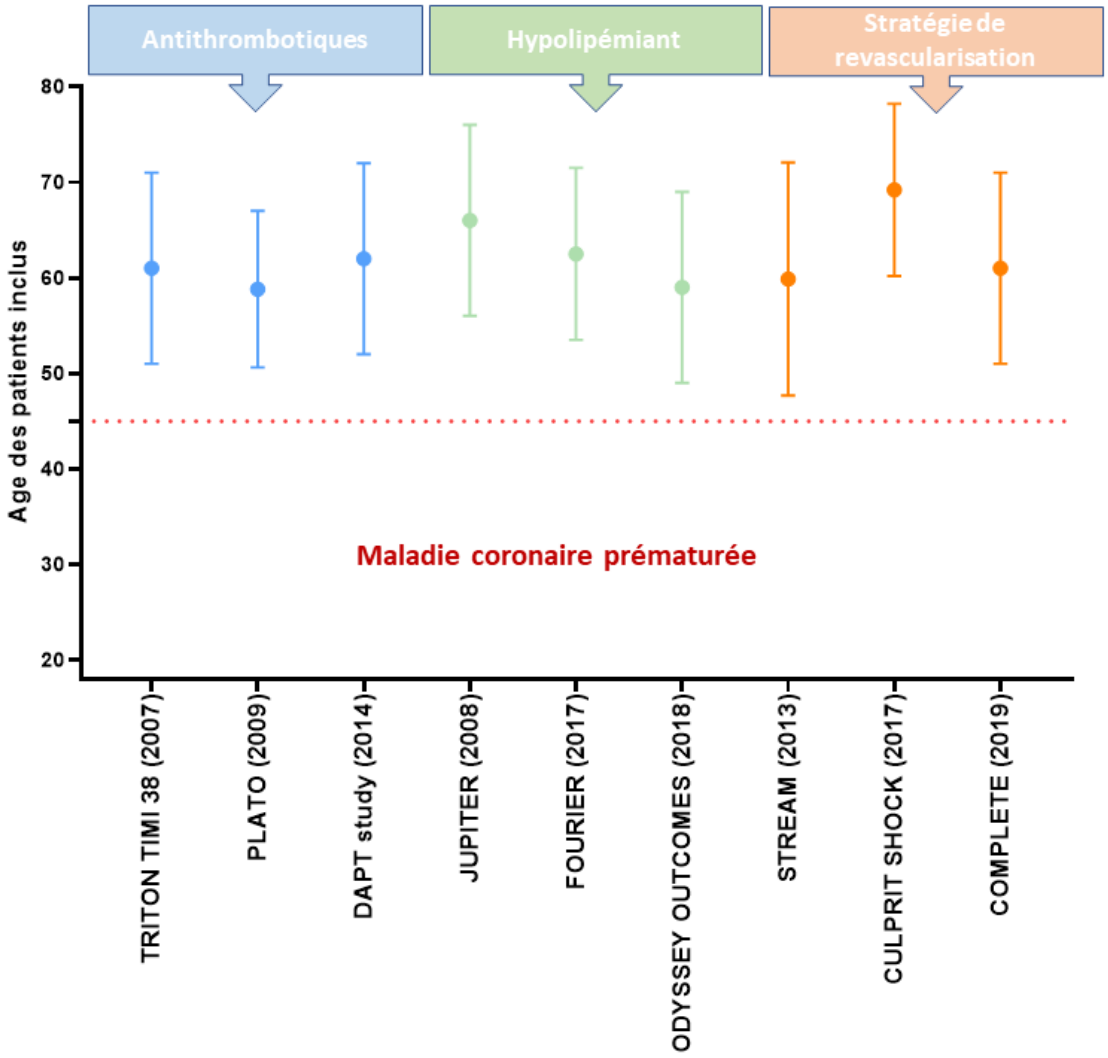

Figure 7. Age moyen avec écart-type des patients inclus dans les essais cliniques de référence en cardiologie

Ainsi, la justification scientifique de cette thèse portant sur l'étude de l'athérosclérose coronaire prématurée s'appuie sur les éléments suivants :

- L'absence de connaissances précises sur les spécificités phénotypiques et biologiques de ces jeunes patients, en particulier en Europe et en Amérique du Nord. Les études présentées plus haut ont démontré que la thrombophilie et de l'hypercholestérolémie familiale n'expliquent la survenue d'une maladie coronaire prématurée que chez une petite proportion de ces patients.

- L'absence de données sur le pronostic à long terme de ces patients. Les données de registre tels que ARIC ne se limitent qu'aux évènements intra-hospitaliers (63, 73). Ces études ont démontré que les jeunes patients sont le seul groupe de patients dont le pronostic immédiat n'a pas été amélioré par l'implémentation des traitements modernes de l'infarctus du myocarde.

- L'absence de description précise de la contribution de l'inflammation à la maladie coronaire prématurée.

- L'absence de stratégie thérapeutique spécifique, que ce soit en prévention cardiovasculaire primaire ou secondaire. Cela est souligné par l'absence de recommandations internationales spécifiques et dédiées à l'athérosclérose prématurée malgré l'élévation de l'incidence de cette pathologie touchant une frange active de la population.

- L'absence de connaissances concernant l'histoire naturelle de l'athérosclérose coronaire et de son évolution sur le long terme. L'étude PROSPECT a démontré que l'évolution des évènements ischémiques coronaires était partagée équitablement entre le site coronaire initiale coupable et des néo-lésions chez les sujets d'âge moyen (74). Ces données ne sont pas connues pour les patients qui développent une maladie coronaire

prématurée, pour qui notre hypothèse est celle d'une évolution plus agressive vers des néo-lésions. Les études que nous présentons dans cette thèse ont ainsi pour objectif d'éclaircir la physiopathologie de l'athérosclérose prématurée, en s'écartant du modèle « d'évènement aigu sur coronaires lisses » pour soutenir l'hypothèse d'une maladie chronique systémique et évolutive impliquant l'inflammation, avec un pronostic global défavorable.

IV. OBJECTIFS DE LA THESE

1. Phénotypes cliniques et biologiques des individus atteints d'athérosclérose prématurée

Etude 1: Collet J-P.*, **Zeitouni M.* (*co-first),** Procopi N., et al. Long-Term Evolution of Premature Coronary Artery Disease. J Am Coll Cardiol 2019;74(15):1868–78. Doi: 10.1016/j.jacc.2019.08.1002 *

Etude 2: Zeitouni M, Clare RM., Chiswell K, et al. Risk Factor Burden and Long-Term Prognosis of Patients With Premature Coronary Artery Disease. Journal of the American Heart Association n.d.;0(0):e017712. Doi: 10.1161/JAHA.120.017712.

La description des différents phénotypes cliniques et biologiques des individus atteints d'athérosclérose prématurée a été l'objectif des études 1 et 2 qui ont respectivement inclus 880 patients français de moins de 45 ans et 3655 patients américains de moins de 50 ans, avec une athérosclérose coronaire décrite objectivement par angiographie coronaire. Sur la base du registre AFIJI **(étude 1)** et de la DDCD **(étude 2),** nous avons pu décrire le profil clinique, le pronostic et les facteurs de risque des patients atteints d'une maladie coronaire prématurée avec un focus particulier sur les nouveaux marqueurs de risques tels que l'ethnie ou la présence d'une maladie inflammatoire chronique. Via un lien entre DDCD et le sous-registre génétique CATHGEN (7), une recherche de mutations responsables d'hypercholestérolémie familiale a pu être effectuée dans l'étude 2. Ces deux études ont pour autre spécificité de décrire un suivi sur le très long terme : jusqu'à 20 ans pour AFIJI, et 10 ans pour DCDD.

2. Contribution de l'inflammation à l'athérosclérose coronaire prématurée et à son pronostic

Etude 3: **Zeitouni M.,** Giamberardino SN., McGarrah R., et al. A novel inflammatory marker of glycosylated proteins is associated with coronary artery disease and incident events with age effect in the PROMISE trial. Journal of the American College of Cardiology 2020;75(11):263. Doi: 10.1016/S0735-1097(20)30890-1 (abstract presented at ACC 2020)

Etude 4 : Silvain J., Kerneis M., **Zeitouni M**., et al. Interleukin-1β and Risk of Premature Death in Patients With Myocardial Infarction. J Am Coll Cardiol 2020;76(15):1763–73. Doi: 10.1016/j.jacc.2020.08.026

L'étude de l'implication de l'inflammation dans la genèse et dans le pronostic de la maladie coronaire prématurée est un élément central de cette thèse. Dans les **études 1 et 2,** l'association entre les maladies inflammatoires chroniques et le pronostic de la maladie coronaire prématurée a été mise en avant. Dans les **études 3 et 4**, la recherche de cette association se place sur un axe plus expérimental et mécanistique, à deux moments différents de la maladie coronaire.

Dans l'**étude 3**, nous avons étudié un nouveau biomarqueur composite de glycosylation des protéines de l'inflammation, et l'amplitude de son association en fonction de l'âge de la découverte d'athérosclérose coronaire. Il s'agit d'une analyse post-hoc pré-spécifiée de l'essai clinique PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), réalisée en collaboration avec le Duke Molecular Physiology Institute (https://dmpi.duke.edu/) (75, 76). Cet essai clinique a inclus des individus sans antécédent cardiovasculaire connu, adressés en consultation pour un angor stable. L'étude a comparé l'efficacité du scanner coronaire contre celle des tests d'ischémie myocardique pour réduire la mortalité et les évènements cardiovasculaires. Une bio-banque a été constituée, incluant en particulier des

échantillons permettant de mesurer un nouveau biomarqueur de l'inflammation chronique : le GlycA.

Le GlycA est un signal composite de tous les signaux de glycosylation des protéines de phase aigüe obtenus en résonance magnétique nucléaire avec spectrométrie **(figure 8)**. La glycosylation des protéines est le processus enzymatique responsable de la fixation de divers glycanes aux protéines de phase aigüe telles que l'α1 -glycoprotéine acide, l'haptoglobine, la transferrine et l'alpha-1 -antitrypsine (77). Cette glycosylation augmente ou diminue en réponse à des stimuli inflammatoires aigus et chroniques et permet de diriger les protéines de phase aigüe vers les différents récepteurs cellulaires et tissulaires concernés. (78–80). Ainsi, le signal GlycA provient des protons du groupe *N*- acétylméthyle des résidus mobiles de glycane des protéines concernées par les processus inflammatoires : les protéines de phase aigüe (81). Le système de résonance magnétique nucléaire développé par la start-up LipoProfile ® additionne de manière automatisée les amplitudes des glycanes mesurées sur le sérum des patients, et permet ainsi de quantifier l'inflammation chronique chez les sujets (82, 83).

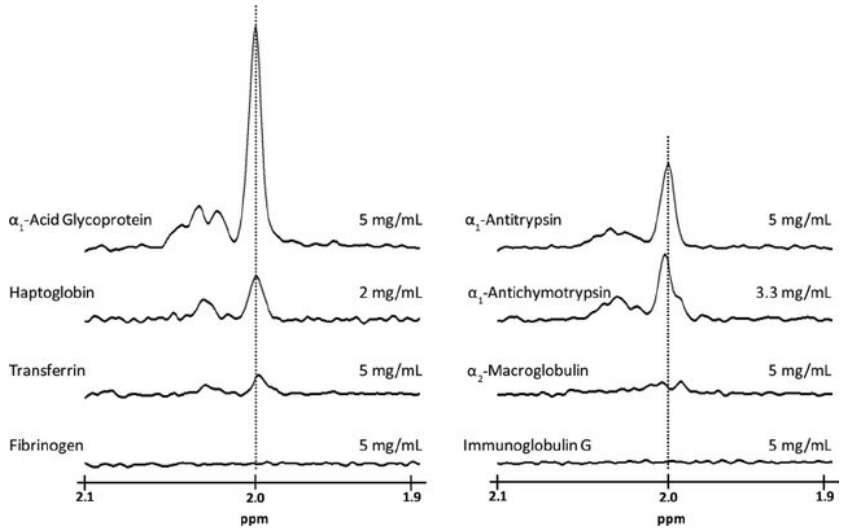

Figure 8. Spectrographie par Résonnance Magnétique nucléaire de la région GlycA de protéines sériques

Adapté de *Otvos et al. GlycA: A Composite Nuclear Magnetic Resonance Biomarker of Systemic Inflammation. Clinical Chemistry 2015;61(5):714–23. Doi: 10.1373/clinchem.2014.232918.*

L’**étude 4** évalue l’association entre la voie de l’interleukine-1-béta (IL-1β) et la mortalité dans les suites immédiates d’un infarctus du myocarde. La voie immunitaire innée de l’IL-1β a suscité un intérêt croissant dans la mesure où des études antérieures ont démontré le rôle central de la cytokine pro-inflammatoire IL-1β dans le processus d'athérothrombose (84, 85). Récemment, l’essai clinique CANTOS a démontré que l'inhibition de l'IL-1 β avec l'anticorps monoclonal humain canakinumab pouvait réduire les récidives d’évènements cardiovasculaires après un IDM et une CRP-us élevée (86). Dans ce contexte, **l’étude 4** avait pour objectif de mesurer les niveaux d’IL-1β au cours d’un infarctus du myocarde et d’évaluer une potentielle association avec la mortalité et les évènements cardiovasculaires majeurs.

3. Mesure expérimentale du vieillissement vasculaire par IRM aortique

Etude 5. Procopi N., Zeitouni M et al. Reduced Proximal Aortic Distensibility is related to recurrent ischemic events in Young Adults with Premature Coronary Artery Disease. Actuellement soumis au JACC.

L’étude 5 a inclus des patients de la cohorte AFIJI afin d’évaluer un nouvel outil de mesure du vieillissement vasculaire, reflétant l’ « âge vasculaire » : la mesure de la distensibilité de l’aorte proximale ascendante par IRM. Cette étude, réalisée en collaboration avec l’unité d’imagerie cardiovasculaire et thoracique de l’Institut de Cardiologie (Pr Redheuil), avait pour objectif de tester ce nouveau marqueur d’imagerie comme facteur pronostique de l’évolution des patients atteints d’une maladie coronaire prématurée.

La distensibilité aortique est un nouvel outil intégratif permettant d’évaluer l’effet de l’athérosclérose calcifiante à un stade infraclinique. Ainsi, dans la cohorte longitudinale MESA composée d’individus sans maladie cardiovasculaire connue, âgés de 45 ans ou plus, la

distensibilité aortique était associée de manière indépendante des facteurs de risque cardiovasculaire à la survenue d'un infarctus du myocarde ou d'un décès cardiovasculaire (87).

Ainsi, **l'étude 5** avait pour objectif d'évaluer ce nouvel outil dans une cohorte d'individus atteints d'une maladie coronaire prématurée, afin de proposer une compréhension multimodale de leur profil vasculaire et de leur risque cardiovasculaire.

4. Evaluation des stratégies et traitements selon les recommandations internationales

Etude 6: Zeitouni M., Nanna MG., Sun J-L., Chiswell K., Peterson ED., Navar AM. Performance of Guideline Recommendations for Prevention of Myocardial Infarction in Young Adults. J Am Coll Cardiol 2020;76(6):653–64. Doi: 10.1016/j.jacc.2020.06.030

Etude 7: Zeitouni M., Sabouret P., Kerneis M., et al. 2019 ESC/EAS Guidelines for management of dyslipidaemia: strengths and limitations. Eur Heart J Cardiovasc Pharmacother n.d. Doi: 10.1093/ehjcvp/pvaa077

L'objectif final de cette thèse était d'évaluer l'efficacité des stratégies de prévention et de traitement, guidées par les recommandations internationales **(études 6 et 7).** Notre hypothèse était que les méthodes de stratification du risque cardiovasculaire utilisées actuellement par les sociétés savantes de cardiologie étaient insuffisantes pour détecter les patients à risque de développer une maladie coronaire ou un infarctus du myocarde prématuré. **L'étude 6** s'appuie sur le registre de la DCDD décrit plus haut, et évalue la performance des recommandations *Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guideline* parue en 2018 pour identifier et traiter les patients à risque de faire un infarctus prématuré (56). Elle évalue aussi l'intensité de la prévention cardiovasculaire secondaire qui leur est adressée après l'infarctus du myocarde.

L'étude 7, publiée sous forme de revue, présente les nouveautés et les limites des nouvelles recommandations européennes *2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)* (57). Cette étude présente également des données sur la performance des recommandations européennes pour identifier et traiter les patients à risque de développer une maladie coronaire prématurée, sur la base de la cohorte AFIJI et e-PARIS.

V. PUBLICATIONS DE LA THESE

Les études référencées pour réaliser les objectifs de cette thèse sont dans le tableau ci-dessous.

Tableau 5 : Études présentées dans la présente thèse

Titre	Institution	Valorisation	Contribution
Long-Term Evolution of Premature Coronary Artery Disease.	Sorbonne Université ACTION UMRS116	Présentation à l'ESC 2019 Publication : JACC (IF 20.59 - Rang A)	Co-premier auteur Recueil de données Protocole de recherche Méthode & Statistiques Ecriture Manuscrit
Risk Factor Burden and Long-Term Prognosis of Patients With Premature Coronary Artery Disease.	Duke Clinical Research Institute Duke Molecular Physiology Institute	Présentation à l'ACC 2020 Publication : JAHA (IF 5.501 - Rang B)	Premier auteur Recherche de Financement Soumission au Comité d'éthique Protocole de recherche Méthode & Statistiques Ecriture Manuscrit
A novel inflammatory marker of glycosylated proteins is associated with coronary artery disease and incident events with age effect in the PROMISE trial.	Duke Molecular Physiology Institute	Présentation à l'ACC 2020 En cours de révision	Premier auteur Recherche de Financement Protocole de recherche Méthode & Statistiques Ecriture Manuscrit
Interleukin-1β and Risk of Premature Death in Patients With Myocardial Infarction.	Sorbonne Université ACTION UMRS116	Présentation à l'AHA 2020 JACC (IF 20.59 - Rang A)	Troisième Auteur Participation à la conception du synopsis Recueil de données et suivi des évènements Révision critique du manuscrit

Association between proximal aorta distensibility and ischemic events in premature coronary artery disease	Sorbonne Université ACTION UMRS116	Présenté à l'ESC 2020 En cours d'écriture	Deuxième auteur Participation à la conception du synopsis Recueil de données et suivi des évènements Révision critique du manuscrit
Performance of Guideline Recommendations for Prevention of Myocardial Infarction in Young Adults	Duke Clinical Research Institute	Présentation à l'ACC 2020 Publication : JACC (IF 20.59 - Rang A)	Premier auteur Recherche de Financement Soumission au comité d'éthique Protocole de recherche Méthode & Statistiques Ecriture Manuscrit
2019 ESC/EAS Guidelines for management of dyslipidaemia: strengths and limitations	Sorbonne Université ACTION UMRS116	Publication: Eur Heart J Cardiovasc Pharmacother (IF =6.7 – Rang A)	Premier auteur Analyse du registre e-Paris Bibliographie Ecriture Manuscrit

1. Long-Term Evolution of Premature Coronary Artery Disease

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ABSTRACT

BACKGROUND. The long-term evolution of premature coronary artery disease (CAD) is unknown.

OBJECTIVES. The objective of this study was to describe the evolution of coronary atherosclerosis in young patients and identify the risk factors of poor outcomes.

METHODS. Participants aged ≤ 45 years with acute or stable obstructive CAD were prospectively enrolled and followed. The primary endpoint was all-cause death, myocardial infarction (MI), refractory angina requiring coronary revascularization, and ischemic stroke.

RESULTS. Eight hundred-eighty patients with premature CAD were included. They were age 40.1 _ 5.7 years, mainly men, smokers, with a family history of CAD or hypercholesterolemia. At baseline presentation, 91.2% underwent coronary revascularization, predominantly for acute MI (78.8%). Over a follow-up of 20 years, one-third (n ¼ 264) of patients presented with a total of 399 ischemic events, and 36% had at least a second recurrent event. MI was the most frequent first recurrent event (n ¼ 131 of 264), mostly related to new coronary lesions (17.3% vs. 7.8%; p ¼ 0.01; hazard ratio [HR]:1.45; 95% confidence interval [CI]: 1.09 to 1.93 for new vs. initial culprit lesion). All-cause death (n ¼ 55; 6.3%) occurred at 8.4 years (median time). Ethnic origin (sub-Saharan African vs. Caucasian, adjusted hazard ratio [adjHR]: 1.95; 95% CI: 1.13 to 3.35; p ¼ 0.02), inflammatory disease (adjHR: 1.58; 95% CI: 1.05 to 2.36; p ¼ 0.03), and persistent smoking (adjHR: 2.32; 95% CI: 1.63 to 3.28; p < 0.01) were the strongest correlates of a first recurrent event. When considering all recurrent events, the same factors and Asian ethnicity predicted poor outcome, but persistent smoking had the greatest impact on prognosis.

CONCLUSIONS. Premature CAD is an aggressive disease despite the currently recommended prevention measures, with high rates of recurrent events and mortality. Ethnicity and concomitant inflammatory disease are associated with poor prognoses, along with insufficient control of risk factors.

ABBREVIATIONS

AFIJI Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention

CABG Coronary Artery Bypass Graft

CAD Coronary Artery Disease

HIV Human Immunodeficiency Virus

MACE Major Adverse Cardiovascular Events

NSTEMI Non ST-Segment Elevation Myocardial Infarction

PCI Percutaneous Coronary Intervention

STEMI ST-Segment Elevation Myocardial Infarction

AdjHR adjusted hazard ratio

INTRODUCTION

Ischemic heart disease accounts for the majority of premature deaths in the world (88). Coronary artery disease (CAD) risk factors explain more than 90% of the attributable risk of CAD, of which nearly half can be reduced by the adoption of a heart-healthy lifestyle (89, 90). However, the incidence of CAD increases in many regions of the world and starts at an earlier age, despite major advances in the prevention and treatment of atherosclerosis (73). The long-term evolution of these young CAD patients in the contemporary era of secondary prevention remains, however, poorly known.

Premature CAD, defined as the occurrence of symptomatic obstructive coronary atherothrombotic lesions before the age of 45 years, has been described in a few registries of limited size, and restricted to the description of the patients baseline characteristics in a retrospective approach (61, 65, 91–94). Neither the long-term outcome nor the precise contribution and evolution of the risk factors have been precisely reported. Such data are critical to know better the burden of CAD and its prognosis under optimal treatment, when the disease starts two decades in advance.

The *Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention (AFIJI)* multicentre prospective cohort was launched in 1996 to better characterize the patient profile, treatment and follow-up of premature CAD in the contemporary era of percutaneous myocardial revascularization, arterial coronary bypass graft (CABG) and potent secondary prevention pharmacotherapy. The goal was also to provide these young patients with optimal cardiovascular prevention measures and follow their evolution after a first unexpected serious cardiac event. We tested the hypothesis whether secondary events were more likely related to new coronary lesion or to the initial culprit lesion.

METHODS

Study design and eligibility

Between April 1, 1996, and June 2017, 880 patients aged less than 45 years who survived the first manifestation of CAD were enrolled in the prospective ongoing AFIJI multicenter cohort study. This program was designed to identify risk factors of premature coronary artery disease and to provide a continuous prospective long-term follow-up (3, 34, 95). Premature CAD was defined as the occurrence of an acute myocardial infarction or a symptomatic myocardial ischemia with an obstructive coronary artery disease (stenosis ≥ 70 %) before the age of 45 years. Myocardial infarction due to non-obstructive coronary artery disease was an exclusion criterion when ischemia or necrosis was not confirmed by cardiac MRI, as well as myocarditis, Tako-Tsubo myocardiopathy and coronary spasm. This prospective study was approved by the local Ethics committee, sponsored by the Assistance Publique-Hôpitaux de Paris, supported and driven by the ACTION Study Group. All patients provided a written informed consent prior to enrolment.

Data collection and follow-up

Baseline characteristics including risk factors, medical history, ethnicity and treatments were reported prospectively as previously described (3, 34, 95). Familial history of CAD was defined as any coronary event that occurred in first-degree relatives before 60 years of age in men and 65 years in women.

Participants were followed-up by general cardiologists with also regular visits to participating tertiary centres (at least once every two years). All information was collected and updated in all patients, presenting or not an event. General follow-up surveys were carried out regularly (2003/2007/2009/2012/2017) to collect additional clinical information including risk factors, symptoms, treatments, regular stress tests and echocardiograms as well as the socio-

professional status. Incentives to participate in educational programs were also launched. In addition to classical risk factors, the presence of chronic inflammatory or immunosuppressive disease such as HIV infection, viral hepatitis or any other chronic inflammatory disease including cancer was recorded. Baseline and repeated coronary angiograms were reviewed by independent investigators at the ACTION study group angiography core laboratory. New ischemic events were classified as being related to the initial treated coronary lesion or to a new lesion on another coronary segment or artery.

Study objectives

The primary study objective was to determine the rate of a first recurrent major adverse cardiovascular event (MACE) at maximal follow-up and the related independent risk factors of MACE. The second objective was to determine whether recurrent events were related to the initial culprit lesion or to the occurrence of new lesions. The third objective was to determine the rate of repeated recurrences and identify their related independent correlates.

Endpoint definitions

The primary endpoint was a composite of all cause death, myocardial infarction, refractory angina leading to coronary revascularization and ischemic stroke. Ischemic stroke was defined as an acute episode of focal or global neurological dysfunction as result of cerebral infarction. Myocardial infarction was defined as type 1 according to the Third Universal Definition of 2012 (96). Secondary endpoints were the individual components of the primary endpoint related to a new lesion site, the occurrence of heart failure (NYHA>2) and major bleedings according to the TIMI definition. Events were adjudicated by physicians not involved in the recruitment and follow-up of patients in the AFIJI program.

Statistical Analysis

Participants were classified according to the occurrence of a first MACE during the follow-up in the study. Continuous variables are presented as mean and standard deviation (SD) or median, as appropriate and compared using Student t-test in case of Gaussian distribution or Mann-Whitney U test in case of non-Gaussian distribution. Categorical variables are presented as counts and percentages and compared using Chi square test or Fisher's exact test in case of low number of events. Cumulative incidence rates were calculated and expressed as the number of new cardiovascular events divided by the number of patient-years of follow-up (number of events per 100 patient-years).

The primary analyses were based on the occurrence of a first MACE. To describe the frequency of cardiovascular events according to time, we used Kaplan-Meier curves for cumulative event-free survival for the prespecified primary endpoint. Follow-up of patients was censored at the 30th of June 2017 irrespective of whether a first recurrent event corresponding to the primary endpoint had occurred. For the first set of analyses, the time to first cardiovascular event was also compared according to whether the event was related to the initial culprit lesion or to a new lesion using log-rank tests.

The secondary analyses involved the time evolution of diabetes and smoking status. Time to recurrences and time to risk factor evaluations were stratified and matched between patients with and without recurrences. For each variable, we evaluated the cumulative exposures from baseline to the first, second or third recurrent event for patients with MACEs, and to the last known status within the corresponding period of time for patients without recurrence. A generalized estimating equation with a trend test was used to assess the differences in the cumulative exposures of each risk factor between patients with or without recurrence.

The third set of analyses assessed the independent factors of recurrences. Because of the time-dependence between risk factors like LDL-C, smoking or diabetes and events, a stratified Cox procedure including these time-dependent covariates was performed to identify the independent variables associated with a first occurrence of MACE. This cox model was stratified according to the time delay from the disease onset to follow-up and recurrent MACE as previously described (97). Variables with a univariate p-value<0.2 as well as age, initial presentation (myocardial infarction or stable coronary artery disease), ethnicity, cardiovascular risk factors (familial history of CAD, active smoking, hypertension and dyslipidemia), LDL-C level, inflammatory disease and revascularization status were included in the model. Eventually, a pooled analysis using repeated measurements with time-dependent covariates was performed to identify the risk factors associated with multiple recurrences. The two-sided significance level was fixed at 5%. All the analyses were performed using the SAS software (9.4, SAS Institute, Cary NC, USA).

RESULTS

Baseline characteristics

Patients were predominantly young males, active smokers, with a frequent family history of CAD and hypercholesterolemia while diabetes was less common. Mean LDL-cholesterol at baseline was 1.69±1.3 g/dL (Table 1). One out of ten patients had a chronic inflammatory or immunosuppressive disease including HIV (4.0%), viral hepatitis (1.3%), systemic auto-immune disease including polyarthritis or systemic lupus with antiphospholipid syndrome (1.3%) and cancer (3.5%) (**Table 1**). Acute myocardial infarction due to single vessel disease with subsequent percutaneous coronary revascularization was the most frequent clinical pattern. Few patients presented with coronary dissection (n=10) or coronary thrombosis after heavy physical exertion (n=11) without underlying stenosis. Secondary prevention treatments were used as recommended per guidelines and did not differ according to the occurrence of MACE (**Table 1**). Fewer patients were exposed to ticagrelor in the MACE group versus the event-free group (5.6% versus 10.1%, p=0.006) and very few patients were on oral anticoagulation (**Table 1**).

Table 1: Baseline patient's characteristics according to occurrence of a first MACE.

Baseline characteristics	Total Population n= 880	Recurrent events n = 264	No recurrent events n=616	P value
Age - year (mean) age – year (median)	40.1 ± 5.7 41.4 (36.5-44.2)	39.6±5.7 41.5 (36.9–44.3)	40.2±5.7 41.1 (36.0-44.0)	0.1
Age < 35 %	160 (18.2%)	58 (22.0%)	102 (16.6%)	
Female gender	117 (13.3%)	33 (12.5%)	84 (13.6%)	0.1
Body mass index (kg/m^2)	26.1 ± 4.3	26.1 ± 4.7	26.1 ± 4.2	
Ethnic group				
White European	638 (72.5%)	189 (71.6%)	449 (72.9%)	0.3
North Africa & Middle East	166 (18.9%)	45 (17.0%)	121 (19.6%)	0.5
Sub-Saharan Africa	46 (5.2%)	16 (6.1%)	30 (4.9%)	0.2
Asian continent	30 (3.4%)	14 (5.3%)	16 (2.6%)	0.02
Admission event				
Myocardial infarction	693 (78.8%)	195 (73.9%)	498 (80.8%)	0.8
Anterior	311 (35.3%)	87 (32.6%)	224 (36.3%)	
Inferior	274 (31.1%)	72 (27.7%)	202 (32.8%)	
Lateral	63 (7.2%)	19 (7.2%)	44 (7.1%)	
Non-specific electric signs	45 (5.1%)	17 (6.4%)	28 (4.5%)	
Stable angina	187 (21.3%)	69 (26.1%)	118 (19.1%)	0.5
Risk factors*				
Familial history of CAD	359 (40.8%)	121 (45.8%)	238 (38.6%)	0.09
Active cigarette smoking	680 (77.3%)	210 (79.6%)*	470 (76.3%)*	0.1
Dyslipidaemia	443 (50.3%)	155 (58.7%)	288 (46.8%)	0.01
LDL-Cholesterol (g/L)	1.69±1.30	1.99±1.46*	1.56±1.20*	0.004
Arterial hypertension	178 (20.3%)	75 (28.4%)	103 (16.7%)	0.002
Diabetes	94 (10.7%)	41 (15.5%)*	53 (8.6%)*	<0.001
Creatinine Clearance (mL/min)	130.3±44.9	126.7 ± 58.8	131.9±37.4	0.3
Chronic inflammatory disease*	87 (9.9%)	45 (17.0%)	42 (6.8%)	<0.001
Coronary artery lesions				
MINOCA**	10 (1.1%)	1 (0.4%)	9 (1.4%)	
One-vessel disease	522 (59.3%)	111 (42.0%)	411 (66.7%)	<0.001
Two-vessel disease	181 (20.6%)	73 (27.7%)	108 (17.5%)	
Three-vessel disease	167 (18.9%)	79 (29.9%)	88 (14.3%)	
Number of lesion / patient	1.6±0.8	1.8±0.9	1.5±0.7	

Table 1 - suite

Baseline characteristics	Total Population n= 880	Recurrent events n = 264	No recurrent events n=616	P value
LVEF*	55.3 ± 9.4	54.2 ± 10.4	55.8 ± 8.9	
Revascularization				
Yes	803 (91.2%)	252 (95.4%)	551 (89.4%)	
CABG	58 (6.6%)	29 (11.0%)	29 (4.7%)	0.02
PCI with DES	452 (51.4%)	126 (47.7%)	326 (52.9%)	0.6
PCI with BMS	293 (33.3%)	97 (36.7%)	196 (31.8%)	0.05
Medical treatment				
Aspirin	858 (97.5%)	257 (97.3%)	601 (97.6%)	0.6
Clopidogrel	528 (60.0%)	189 (71.6%)	339 (55.0%)	0.006
Ticagrelor	80 (9.1%)	18 (6.8%)	62 (10.1%)	0.006
Prasugrel	132 (15.0%)	32 (12.1%)	100 (16.2%)	0.1
Statins	820 (93.2%)	243 (92.0%)	577 (93.7%)	0.2
Beta-blockers	786 (89.3%)	238 (90.2%)	548 (89.0%)	0.1
ARB / ACE-inhibitors	683 (77.6%)	213 (80.7%)	470 (76.3%)	0.2
Oral anticoagulants	50 (5.7%)	16 (6.1%)	34 (5.5%)	0.4

Footnote: CAD stands for coronary artery disease, LDL-Cholesterol for low-density lipoprotein cholesterol, MINOCA for myocardial infarction with non-obstructive coronary artery disease, LVEF for left ventricle ejection fraction, CABG for coronary artery bypass grafting, PCI for percutaneous coronary intervention, DES for drug-eluting stent, BMS for bare-metal stent, ARB for angiotensin II receptor blockers, ACE-inhibitors for Angiotensin converting enzyme inhibitors. *corresponds to the values observed before the first recurrence. * *Human immunodeficiency virus (n=34), viral hepatitis (n=10), HIV-Hepatitis C co-infection (n=1) cancer (n=31) or systemic auto-immune disease (n=11)* ** Only when confirmed by cardiac MRI.

Time to first event analyses

Detailed cardiovascular outcomes and vital status were obtained for all patients, except for five patients who were lost to follow-up (0.57%). The description of lipid-lowering therapies along follow-up and dual antiplatelet therapy durations are displayed in **online table 1 and 2.**

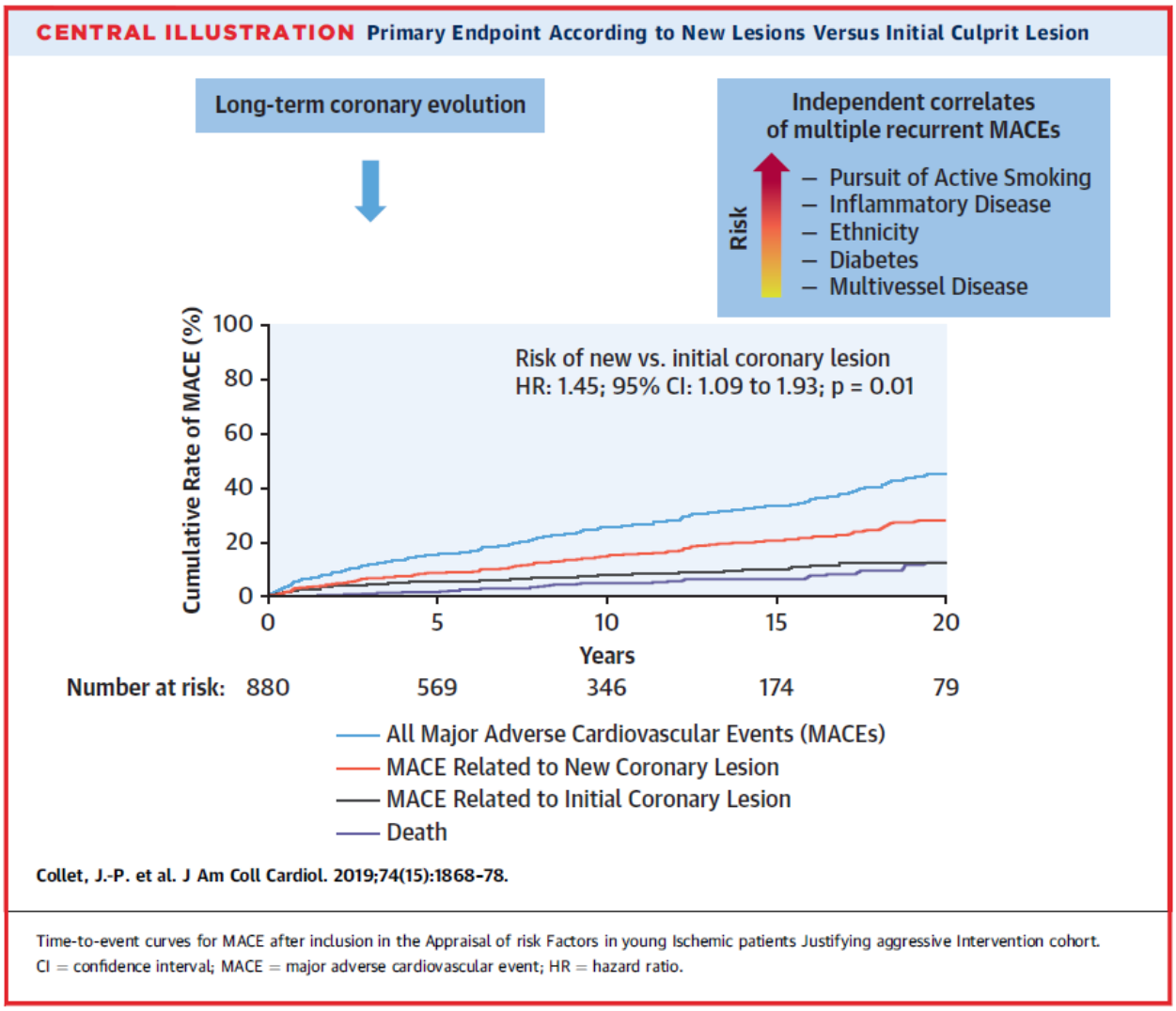
Over the 20-year follow-up, 30% of patients (n=264) presented a total of 399 MACEs corresponding to 4.68 (4.23-5.18) events per 100 patient-years **(Table 2).** Myocardial infarction was the most frequent first recurrent event (2.6 per 100 patient-years) while all-cause death (1.60 per 100 patient-years) and stroke (0.70 per 100 patient-years) were less frequent.

Table 2: Major adverse cardiovascular events.

	1st recurrence **n=264/880 (30.0%)**	**Time in years** **median, (25th and 75th percentile)**	**2nd recurrence** **n=81/225* (36.0%)**	**Recurrences ≥ 3** **n=54/70** (77.1%)**	**Total Events Counts**
All-cause Death	39 (4.4)	8.4, (3.2-15.9)	11 (4.9)	5 (7.1)	55
Myocardial Infarction	131 (14.9)	3.7, (0.8 -7.8)	40 (17.8)	38 (54.3)	209
STEMI	47 (5.3)	4.1, (0.8-7.9)	10 (4.4)	12 (17.1)	69
NSTEMI	84 (9.5)	3.5, (0.7-7.7)	30 (13.3)	26 (37.1)	140
Refractory Ischemia requiring revascularization	88 (10.0)	5.1, (1.4-11)	28 (12.4)	11 (15.7)	127
PCI	66 (7.5)	6.3, (1.7-10.7)	18 (8.0)	2 (2.9)	85
CABG	22 (2.5)	2.8, (0.9-12.3)	10 (4.4)	9 (12.9)	41
Ischemic Stroke	6 (0.7)	5.4, (1.8-8.4)	2 (0.9)	0 (0)	8
Primary endpoint	264 (30.0)	4.2, (1.3-9.8)			4.68 (4.23-5.18) events per 100 patient-years

Footnote: * (%) is the percentage of patients with a second recurrent MACE out of patients who had a first non-fatal recurrent MACE; ** (%) is the percentage of patients with 3 or more recurrent MACE out of patients with a second non-fatal second recurrent MACE. STEMI stands for ST-segment elevation Myocardial Infarction, NSTEMI for Non-ST-segment elevation myocardial infarction, PCI for Percutaneous Coronary Intervention, CABG: coronary artery bypass grafting.

The first non-fatal recurrent ischemic event was related to a new lesion site in 152 patients and to the initial culprit lesion in 69 patients (17.3% vs 7.8%, p=0.01, HR=1.45, 95% CI [1.09; 1.93] for new versus initial lesion, respectively**) (Central illustration).** Among the 522 patients with single coronary vessel disease at baseline, 112 evolved towards symptomatic multivessel disease. Death as the first recurrent event was three times less frequent than myocardial infarction and occurred at a much later stage (8.4 vs. 3.7 years). Stroke occurred in less than 1% of patients (**Table 2**).



Time-to-event curves for MACE after inclusion in the Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention cohort. CI = confidence interval; MACE = major adverse cardiovascular event; HR = hazard ratio.

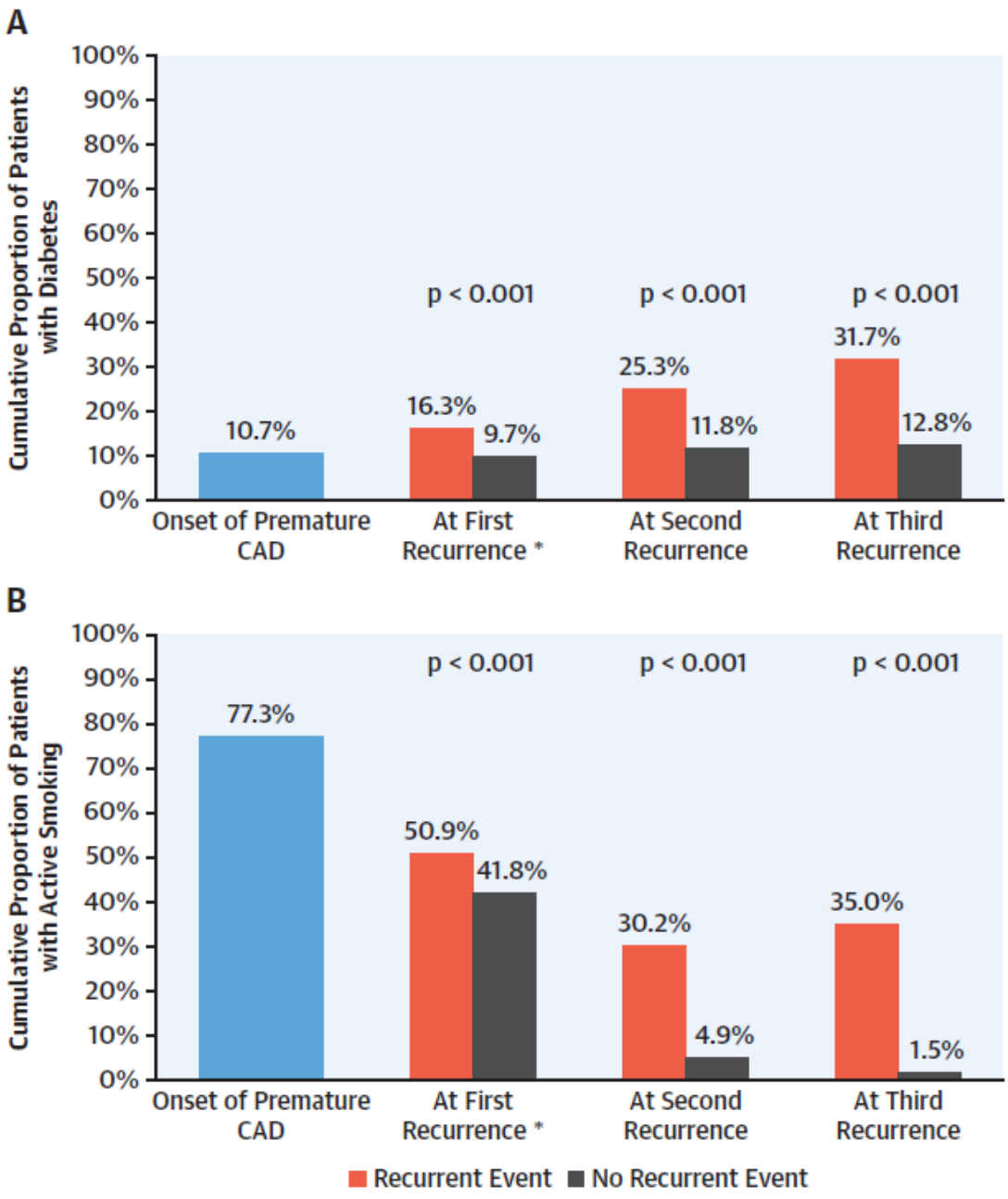
Patients with a first MACE were more likely to have uncontrolled risk factors with more frequent active smoking, diabetes, and with a higher LDL-cholesterol level prior to the first recurrent event; they were also more likely to be of Sub-Saharan Africa or of Asian origin **(Table 1).** Patients with multivessel disease were also more likely to suffer from an ischemic recurrence, as well as patients initially treated by CABG.

Twenty-one patients (2.4%) developed severe heart failure, five patients underwent heart transplantation and thirteen had a major bleeding. More than one third of the patients of the AFIJI registry (295/880) had an event during follow-up as defined according to secondary endpoints.

Time to second or third recurrence

Of the 255 patients with a first non-fatal recurrence, 81 patients (36.0 %) had at least a second recurrent MACE **(table 2).** The continuous monitoring of risk factors showed more frequent new diabetes and a greater exposure to active smoking before each recurrent MACE **(Figure 1 A and B).** The exposure to active smoking decreased but remained high in patients with multiple recurrences (from 50.9% to 35.0%) compared with patients free or ischemic recurrences (41.8% to 1.5%). Interestingly, one out of three patients with multiple recurrences eventually developed diabetes as compared to one out of ten among event-free patients.

FIGURE 1 Cumulative Exposure to Time-Dependent Major Risk Factors According to the Occurrence of Major Cardiovascular Events: New Onset of Diabetes and Smoking Status



*Time delays to recurrences and to risk factor evaluations were stratified and matched between patients with recurrences and patients without recurrences. Cumulative rates of diabetes **(A)** and active smoking **(B)** in patients with ischemic recurrences from baseline to first, second, or third recurrence is compared with the cumulative rate of each risk factor in patients without ischemic recurrence, from baseline to last known status, within a corresponding period of time.

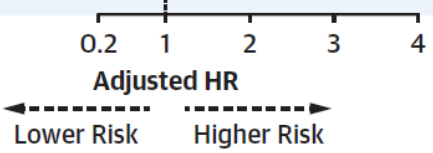
Independent risk factors of poor outcome

The multivariate stratified Cox regression model based on repeated measurements with time-dependent covariates demonstrated that persistent smoking was the greatest correlate of a first recurrent event (adjHR: 2.32, 95% [1.63-3.28], p<0.01). Ethnic origin, (sub-Saharan African vs Caucasian, adjHR: 1.95, 95% CI [1.13-3.35], p=0.02), diabetes, (adjHR: 1.75, 95%CI [1.20 – 2.55], p<0.01) as well as chronic inflammatory disease (adjHR: 1.58 95%CI [1.05-2.36], p=0.03 and multivessel disease at baseline were strong independent risk factors of a first recurrent MACE. When considering all recurrent events, the same factors plus hypertension and Asian ethnicity predicted poor outcome, but persistent smoking had by far the strongest impact on prognosis (adjHR: 2.70, 95% CI [2.05-3.55], p<.001) (**Figure 2 A and B**).

FIGURE 2 Hazard Ratio Plot of Multivariate Stratified Cox Model Using Repeated Measurements

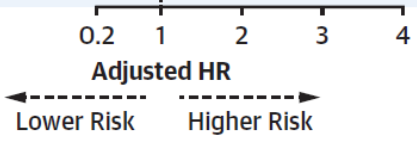
A

	Adjusted HR [95% CI]	p Value
Women	0.68 [0.46-1.03]	0.07
Age (per 1 year)	0.95 [0.96-1.01]	0.17
ACS at presentation	1.05 [0.77-1.43]	0.78
Ethnic group*		
Asian	1.38 [0.77-2.49]	0.28
North African and Middle Eastern	0.83 [0.58-1.18]	0.29
Sub-Saharan African	1.95 [1.13-3.35]	0.02
Risk Factors		
Diabetes	1.75 [1.20-2.55]	< 0.01
Familial history of CAD	1.11 [0.84-1.47]	0.45
Hypertension	1.21 [0.90-1.62]	0.21
LDL-C (per 1 g/L)	1.07 [0.97-1.18]	0.18
Pursuit of active smoking	2.32 [1.63-3.28]	< 0.01
Inflammatory disease	1.58 [1.05-2.36]	0.03
Multivessel disease	1.71 [1.28-2.28]	< 0.01



B

	Adjusted HR [95% CI]	p Value
Women	0.84 [0.59-1.21]	0.35
Age (per 1 year)	0.99 [0.97-1.01]	0.28
ACS at presentation	0.88 [0.66-1.16]	0.35
Ethnic group*		
Asian	1.56 [0.98-2.49]	0.06
North African and Middle Eastern	0.91 [0.67-1.24]	0.55
Sub-Saharan African	1.64 [1.07-2.52]	0.02
Risk Factors		
Diabetes	1.48 [1.12-1.96]	< 0.01
Familial history of CAD	1.11 [0.88-1.40]	0.39
Hypertension	1.21 [1.02-1.69]	0.03
LDL-C (per 1 g/L)	1.07 [0.96-1.14]	0.31
Pursuit of active smoking	2.70 [2.05-3.55]	< 0.01
Inflammatory disease	1.74 [1.29-2.35]	< 0.01
Multivessel disease	1.44 [1.12-1.85]	< 0.01



DISCUSSION

The AFIJI cohort provides a prospective description of the contemporary long-term evolution of coronary atherothrombosis occurring in a cohort of young patients. Recurrent events were frequent, occurred early in the course of the disease and were mainly due to new coronary lesions. Insufficient control of modifiable risk factors, concomitant chronic inflammatory disease and Asian/sub-Saharan ethnicities were the major factors associated with a poor prognosis. Our findings shed light on where our efforts should focus to blunt this unfavourable evolution in one out of three patients who presented a first event before the age of 45 years.

All patients of the AFIJI registry were all-comers screened during hospital stay or at the outpatient clinic of the investigating centres. Most patients had angiographically established CAD with and most of them presented with ST-elevation myocardial infarction. The few who did not undergo coronary revascularization presented with a myocardial infarction due to a coronary dissection (mostly in women) or to acute coronary thrombosis without significant underlying coronary stenosis. The high rate of recurrent myocardial infarction in the AFIJI registry demonstrates that premature CAD is an evolving disease. This high rate of ischemic events persisted through the different therapeutic eras, in spite of the advent of drug eluting stents, potent $P2Y_{12}$ inhibitors and second-generation statins (Online Figure 1). Half of recurrences occurred within the first 4 years and 75% within the first 10 years of follow-up. Most of the secondary prevention trials testing the long-term benefits of secondary prevention interventions reported lower event rates than AFIJI, certainly because of a less aggressive disease in older patients, a shorter follow-up of these studies and consideration of the first recurrent event only (98–101) (online table 5). Remarkably, the first recurrent MACE on optimal secondary prevention occurred before the age of 60 in 98% of our patients, an age corresponding to the median age of CAD revelation in the general population.

Multivessel disease at baseline was logically an independent predictor of first recurrence and multiple recurrences. This was also true for patients who underwent CABG surgery with recurrent events in more than half of them. The progression of atherothrombosis from single to multivessel disease paralleled the number of recurrences. The PROSPECT study reported that major recurrent events were equally distributed between culprit and non-culprit lesions and we report here that new coronary lesions were involved in 2 out of 3 patients suggesting a fast progression of the disease in these young patients (74). This aggressive progression towards new lesion sites demonstrates the need for non-invasive multi-modal strategies able to capture the evolution and instability of subclinical atherosclerosis in young patients (102). Among the promising technical advances, computed tomography angiography have enabled to describe the remodeling and necrotic aspects of plaques and relate them to the risk of coronary events (103).

Poor control of cardiovascular risk factors is obviously of paramount prognostic importance. One out of two patients was still an active smokers at the time of the first recurrence, a rate that is consistent with recent European surveys (104). A 7-fold decrease of active smoking was obtained with education programs but still 11% of the patients were active smokers at the end of our follow-up. Our data indirectly confirm that smoking cessation is the most efficient secondary prevention measure, especially before the age of 40 years (105). The other modifiable risk factors –diabetes and hypertension – were also independently associated with multiple recurrent MACEs, emphasizing the need for an aggressive secondary prevention in this population. Larger infarct size, poor recovery from myocardial injury, comorbidities and persistent inflammation are the known consequences of persistent active smoking triggering coronary recurrences, heart failure and cardiovascular death (106, 107). The average level of LDL cholesterol in these young patients was noticeably higher than the average usual MI population (108). Although improving over time, the proportion of patients with on-treatment LDL cholesterol plateau levels above 0.7 g/L was high, suggesting unrecognized heterozygous

familial hypercholesterolemia but also insufficient treatment intensity (online Table 1). (50, 109). The increasing proportion of new onset of diabetes over time in patients with recurrent adverse event is another intriguing finding which indicates partial failure of our behavioral programs with respect to physical activity and diet.

The 10% of patients with chronic inflammatory disease had accelerated atherothrombosis with more frequent recurrent events. Chronic inflammation together with the cardiometabolic effects of corticosteroids or antiretroviral drugs may have participated to CAD progression. High platelet reactivity on P2Y12 inhibitors and potential drug-drug interactions are also additional explanatory factors (110). Ethnicity is a non-modifiable risk factor involving both genetics and habits - that impacted long-term outcomes of young patients (111). Young sub-Saharan African patients carried the higher burden of cardiovascular disease. Previous similar findings have associated this higher risk with a more frequent hypertension, diet habits and unequal access to prevention and healthcare (112). Asian ethnicity is particular to the AFIJI registry recruitment with patients originating from south-east Asia where the prevalence of diabetes and multivessel disease is high. Several Indian and South-east Asian registries have described an early onset of coronary artery disease, with a median age of 55 years old compared to 65 years old in western countries (113).

Ethnicity, chronic inflammatory disease, familial history of premature CAD and early menopause have been listed as risk-enhancers in the American guidelines on blood cholesterol management (56). The present results display additional evidence and variables to support tailored secondary prevention strategies for these young patients. Non-invasive imaging methods to better predict the potential evolution of the non-culprit coronary plaques in these specific subgroups needs further investigation. In particular, CT scan data combined with deep phenotyping including LDL-cholesterol on statin therapy may further help refinement of the intensity of lipid-lowering therapies with dedicated machine learning algorithms (56, 114, 115).

Whether we can improve the long-term prognosis of these patients is a pending issue. Better control of the risk factors and treatment adherence are known challenges for secondary prevention. It is likely that a more aggressive secondary prevention using PCSK9 inhibitors and new antidiabetic drugs, which reduce both MACE and mortality, would be of incremental value in this high-risk population with frequent dyslipidemia and new onset of diabetes (116–118). Lifestyle changes is often difficult to obtain but the potential benefit of the Mediterranean diet and physical activity are well demonstrated (89, 119). The residual risk related to chronic inflammation is another target in this young population. Interleukin-1β inhibition with canakinumab was effective in reducing cardiovascular events in a different high-risk atherosclerosis population, particularly those with elevated markers of inflammation (120). Anti-inflammatory therapy may have cardiovascular efficacy in AFIJI-type patients considering the independent risk prediction of inflammatory disease we observed. Whether tailored therapy according to inflammatory biomarkers may improve outcome of these young patients needs to be addressed.

LIMITATIONS

There are several limitations inherent to this long-term prospective registry. First, advances in secondary pharmacological prevention treatment and in myocardial revascularization technology may have created a time-confounding bias not entirely addressed by the use of time-dependent variables and the time-stratified cox model. Similarly, statistical modelling could only partially balance the discrepancies in the measurement of time-dependent variables between patients with and without recurrent events. Second, asymptomatic patients did not undergo systematic coronary imaging investigations and we may have underestimated progression of the disease in some of these patients. Third, this AFIJI cohort outlines the role of ethnicity which may be confounded by other socio-economic factors. Finally, changes in

physical activity or diet were not captured in this survey as well as psychological traits, all being additional prognostic factors of coronary disease.

CONCLUSIONS

Premature coronary artery disease is a chronic and aggressive disease, with a high rate of recurrences and a rapid evolution towards multivessel disease. Ethnicity and chronic inflammation, along with traditional modifiable risk factors including pursuit of smoking and new onset of diabetes appear to be important factors of poor outcomes. Intensification of the current secondary prevention measures is desirable to prevent the evolution of the disease towards multivessel disease, repeated coronary events and heart failure.

PERSPECTIVES

Competency in Medical Knowledge: Premature coronary artery disease carries a high-risk burden compared with atherothrombosis in middle-aged patients.

Translational Outlook: Ethnicity, chronic inflammation and behavior-related risk factors are the most important contributors of poor prognosis in these young CAD patients. Specific programs directed towards behavioral changes and management of biological risk factors including inflammation should be tested.

ONLINE SUPPLEMENT

Online table 1: Lipid-lowering therapy along follow-up according to number of recurrent MACEs.

	Baseline	No MACE	Admission MACE 1	Admission MACE 2	Admission MACE 3
High-intensity statin	64.8%	54.0%	52.0%	49.0%	34.6%
Moderate-intensity statin	28.5%	35.1%	30.4%	37.7%	46.1%
Low-intensity statin	1.7%	8.1%	10.5%	3.7%	7.7%
No statin	5.0%	2.7%	7.2%	9.4%	11.5%
Ezetimibe	5.4%	10.8%	17.1%	7.5%	7.7%

MACE stands for major adverse cardiovascular event

Online table 2: Dual antiplatelet therapy (DAPT) duration along follow-up according to number of recurrent MACEs.

DAPT duration (years)*	**DAPT stopped before the end of the study n= 479**	**Sustained DAPT at the end of the study n= 227**
Median (25th and 75th percentile)	1.25 (1.0 - 3.6)	5.2 (2.3 - 11.4)
Mean (SD)	3.3 (4.6)	7.5 (6.6)

MACE stands for major adverse cardiovascular event. *data available for 706 patients

Online Table 3: Pooled analysis using repeated measurements of time-dependent covariates for first recurrence with time-stratified cox model.

	Univariate time dependent covariates Cox model			Multivariate time dependent covariates Cox Model*		
Variables	**N***	**Hazard-ratio (95% CI)**	**P-value**	**N***	**Hazard-ratio (95% CI)**	**P-value**
Age (years)	1750	0.98 (0.96;1.00)	0.0920	1566	0.98 (0.96;1.01)	0.1783
MI vs Stable CAD at initial presentation	1750	0.98 (0.74;1.30)	0.8965	1566	1.05 (0.77;1.43)	0.7755
Ethnic origin						
Asian vs. Caucasian	1750	1.80 (1.19;2.71)	0.0050	1566	1.38 (0.77;2.49)	0.2838
North Africa & Middle East vs. Caucasian	1750	0.89 (0.65;1.21)	0.4614	1566	0.83 (0.58;1.18)	0.2906
Sub-Saharian African vs. Caucasian	1750	1.41 (0.82;2.41)	0.2098	1566	1.95 (1.13;3.35)	0.0163
Familial history of CAD	1750	1.30 (1.02;1.67)	0.0353	1566	1.11 (0.84;1.47)	0.4460
Diabetes	1750	1.91 (1.37;2.66)	0.0001	1566	1.75 (1.20;2.55)	0.0039
Hypertension	1750	1.47 (1.13;1.90)	0.0036	1566	1.21 (0.90;1.62)	0.2112
LDL cholesterol (g/L)	1566	1.15 (1.05;1.25)	0.0029	1566	1.07 (0.97;1.18)	0.1802
Inflammatory disease	1750	1.60 (1.12;2.29)	0.0102	1566	1.58 (1.05;2.36)	0.0272
Active smoking before first recurrence	1750	2.32 (1.74;3.09)	<.0001	1566	2.32 (1.63;3.28)	<.0001
Multivessel disease	1750	2.18 (1.69;2.80)	<.0001	1566	1.71 (1.28;2.28)	0.0003
Revascularization	1750	1.70 (0.94;3.06)	0.0787	1566	1.60 (0.81;3.14)	0.1726
Women	1750	0.68 (0.46;1.03)	0.0658			

**N refers to the total number of observations along the entire follow-up.*

Online Table 4: Pooled analysis using repeated measurements of time-dependent covariates for multiple recurrences with time-stratified cox model.

	Univariate time dependent covariates Cox model*			Multivariate time dependent covariates Cox Model†		
Variables	**N***	**Hazard-ratio (95% CI)**	**P-value**	**N***	**Hazard-ratio (95% CI)**	**P-value**
Age (years)	2625	0.99 (0.97;1.01]	0.1969	2364	0.99 [0.97-1.01]	0.2766
MI vs. stable CAD at initial presentation	2625	0.95 (0.72;1.25]	0.7080	2364	0.88 [0.66-1.16]	0.3529
Ethnic origin						
– Asian vs. Caucasian	2625	1.77 (1.15;2.74]	0.0098	2364	1.56 [0.98-2.49]	0.0625
– North Africa & Middle East vs. Caucasian	2625	0.94 (0.69;1.28]	0.7020	2364	0.91 [0.67-1.24]	0.5460
– Sub-Saharian African vs. Caucasian	2625	1.56 (0.96;2.55]	0.0735	2364	1.64 [1.07-2.52]	0.0234
Familial History of CAD	2625	1.24 (0.99;1.55]	0.0576	2364	1.11 [0.88-1.40]	0.3937
Diabetes	2625	1.65 (1.26;2.15]	0.0002	2364	1.48 [1.12-1.96]	0.0057
Hypertension	2625	1.72 (1.36;2.16]	<.0001	2364	1.31 [1.02-1.69]	0.0340
LDL cholesterol (g/L)	2364	1.16 (1.07;1.26]	0.0002	2364	1.05 [0.96-1.14]	0.3110
Inflammatory disease	2364	1.16 (1.07;1.26]	0.0002	2364	1.05 [0.96-1.14]	0.3110
Multivessel disease	2625	1.87 (1.48;2.37]	<.0001	2364	1.44 [1.12-1.85]	0.0039
Revascularization	2625	2.46 (1.39;4.33]	0.0019	2364	2.19 [1.11-4.29]	0.0230
Active smoking	2625	2.81 (2.21;3.58]	<.0001	2364	2.70 [2.05-3.55]	<.0001
Women	2625	0.84 (0.59;1.21]	0.3531			

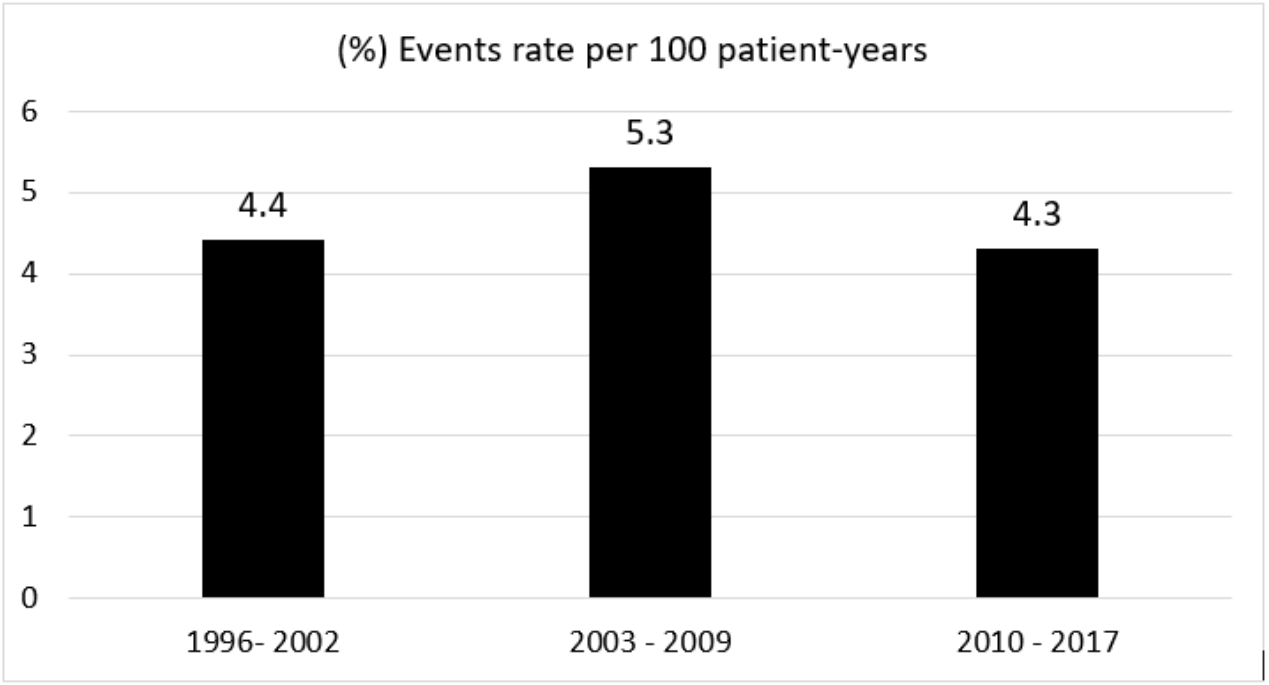
**N refers to the total number of observations along the entire follow*

Online Table 5: Incidence of events in the AFIJI cohort compared to similar cohorts.

	AFIJI CAD<45	PROSPECT ACS/PCI	DAPT CAD/PCI	Young-MI registry	ARIC Surveillance Study	AMERICA CAD>75
Mean age	40	58	62	45	48	77
Prior MI	80%	96%	26%	57.4 %	26.8 %	80%
Prior PCI	85%	100%	100%	-	23.6%	77%
Active smokers	77%	48%	21%	52.3 %	52.9 %	14%
Diabetes	11%	17%	31%	16.7 %	30.3 %	24%
Multivessel disease	39%	79%	NA	-	-	58%
Events rate per 100 patient-years	2.2**	1.48**	1.56**	1.1*	0.5*	5.8**

Footnote : * rate of death ** rate of death and myocardial infarction,

Online figure 1: Rate of major adverse cardiovascular events according to period of inclusion



2.Risk factor burden and long-term prognosis of patients with premature coronary artery disease

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ABSTRACT

BACKGROUND. Coronary artery disease (CAD) is increasing among young adults. We aimed to describe the cardiovascular (CV) risk factors and long-term prognosis of premature CAD.

METHODS. Using the Duke Databank for Cardiovascular Disease, we evaluated 3655 patients admitted between 1995 to 2013 with a first diagnosis of obstructive CAD before the age of 50 years. Major adverse cardiac events (MACE), defined as the composite of death, myocardial infarction, stroke or revascularization were ascertained for up to 10 years. Cox proportional hazard regression models were used to assess associations with the rate of first recurrent event, and negative binomial loglinear regression was used for rate of multiple event recurrences.

RESULTS. Past or current smoking was the most frequent CV factor (60.8%), with hypertension (52.8%) and family history of CAD (39.8%). Within a 10-year follow-up, 52.9% of patients had at least one MACE, 18.6 % had at least two recurrent MACEs and 7.9 % had at least three recurrent MACEs, with death occurring in 20.9% of patients. Across follow-up, 31.7% to 37.2% of patients continued smoking, 81.7 % to 89.3 % had LDL-C levels beyond the goal of 70 mg/dL and 16% had new-onset diabetes. Female sex, diabetes mellitus, chronic kidney disease, multivessel disease and chronic inflammatory disease were factors associated a recurrent MACE.

CONCLUSIONS. Premature CAD is an aggressive disease with frequent ischemic recurrences and premature death. Individuals with premature CAD have a high proportion of modifiable CV risk factors, but failure to control them is frequently observed.

Keywords: premature coronary artery disease; cholesterol; heterozygous familial hypercholesterolaemia; long term evolution

ABBREVIATIONS

HeFH heterozygous familial hypercholesterolemia

DDCD Duke Databank for Cardiovascular Disease

PCI percutaneous coronary intervention

CAD coronary artery disease

apoB apolipoprotein B

LDL-R Low Density Lipoprotein Receptor

PCSK 9 Proprotein Convertase Subtilisin/Kexin Type 9

INTRODUCTION

Despite improvements in preventive therapies, recent North American registries have indicated an increase in young patients admitted for premature myocardial infarction (MI) (63, 73). This trend was more commonly observed in women less than 50 years old, for whom the incidence of hospitalization for acute myocardial infarction has nearly doubled over the last 20 years. Little evidence exists about the characteristics of individuals with premature CAD as well as the contribution of traditional cardiovascular risk factors and the efficacy of modern secondary prevention (93, 113).

Recent studies have described the association between active smoking and other non-traditional risk factors such as ethnicity or inflammation on the prognosis of patients with premature CAD (121). Other studies have linked heterozygous familial hypercholesterolemia (HeFH) with the diagnosis of atherothrombosis in these young individuals (50). Overall, more efforts are needed to understand the risk profile and behaviors of young individuals, as well as the natural history of their atherosclerotic heart disease. This is of paramount importance, in terms of life-years saved for a population who is professionally active and for whom theoretical life expectancy exceeds 20 years.

We hypothesized that patients with young premature MI had a high rate of multiple ischemic events, and an unfavourable control of cardiovascular risk factors along time. Thus, using the Duke Databank for Cardiovascular Disease (DDCD), a large longitudinal registry of patients undergoing cardiovascular testing at Duke University Health System, our objective was to the describe the baseline and follow-up risk factors of patients admitted with premature (under 50 years old) coronary artery disease (CAD) in North Carolina, and to evaluate their long-term prognosis.

METHODS

Study design and population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study population consisted of patients enrolled in the Duke Databank for Cardiovascular Disease (DDCD) for a first manifestation of obstructive coronary artery disease before the age of 50 years old from 1995 to 2013. The design of the DDCD has been previously described; in brief, it is a prospective registry with a pre-specified data collection of clinical and angiographic baseline characteristics of all patients undergoing cardiac catheterization at Duke University Medical Center between (122–124).

Obstructive coronary artery disease was defined as a coronary stenosis > 50 % in an epicardial vessel. Patients with prior documented CAD and those previously treated with percutaneous coronary intervention (PCI) or coronary artery bypass graft were excluded, as were patients that did not have follow-up for more than 1 year.

This retrospective observational study was approved by the Duke Institutional Review Board under a waiver of informed consent and Health Insurance Portability and Accountability Act of 1996 approval.

Data collection and follow-up

Baseline clinical characteristics, risk factors and angiographic findings were collected from both DDCD and Duke Health System records according to pre-specified methods (122–125). Baseline clinical characteristics included traditional cardiovascular risk factors, kidney function, comorbid conditions such as HIV, cancer, connective tissue disease and medications at discharge. Baseline angiographic descriptions included coronary dominance, coronary anatomy, and burden of disease including number and localization of vessels with significant stenosis. Genetic data about mutations related to familial hypercholesterolemia were obtained in

a subset of 9300 individuals via a linkage with CATHGEN, which is a sub-registry of DDCD (7). Coding variants within the apolipoprotein B (*APOB*), Low Density Lipoprotein Cholesterol Receptor (*LDLR*) and Proprotein Convertase Subtilisin/Kexin Type 9 (*PCSK9*) genes were annotated and determined as pathogenic or likely pathogenic based on the American College of Medical Genetics (ACMG) criteria.

Follow-up of vital status, ischemic events and cardiovascular risk factors was performed in DDCD until 2014. Using a prespecified protocol, DDCD consistently ascertained follow-up of patients with significant CAD, including both Duke and non-Duke hospitalization adverse events and smoking exposure (usual number of cigarettes smoked/day in past 6 weeks), via an annual follow-up telephone call or mailed survey. Mortality follow-up was supplemented by a query of the National Death Index for patients with unknown vital status. The Duke Health System records were also extracted for analysis of follow-up LDL-C values and new occurrences of diabetes mellitus, in patients with follow up at Duke.

Clinical Endpoints

The primary objective was to determine the rate of major adverse cardiovascular events (MACE) in patients with premature CAD, during an up to 10 years of follow-up. MACEs were defined as the composite of all-cause death, non-fatal myocardial infarction, revascularization by percutaneous coronary and CABG, or stroke. The second objective was to determine the factors associated with time to a first recurrent MACE and the factors associated with the rate of multiple recurrent MACE events. A third objective was to evaluate the control of traditional cardiovascular risk factors after index catheterization in the population of patients with discrete follow up data. Patients surveyed as smoking >0 cigarettes/day were classified as currently smoking at survey date. Cholesterol control was defined as LDL-C<70 mg/dL according to the latest American Heart Association/American College of Cardiology 2018 Cholesterol Clinical

Practice Guidelines (126). A sensitivity analysis was performed using an LDL-C threshold of 100 mg/dL. New diagnosis of diabetes mellitus was determined by presence of a relevant billing diagnostic code (ICD-9 250.x) in Duke Health System records.

Statistical methods

Participants were classified according to age categories at presentation [extremely premature ≤ 35 years-old, very premature > 35 – 45 years, and premature > 45 – < 50 years old]. Continuous variables are presented as median and interquartile ranges and compared across groups using a Kruskal-Wallis test. Categorical variables are presented as counts and percentages and compared using a Chi square test or Fisher's exact test in the case of low number of events. Except for death, non-fatal ischemic events occurring within 30 days of the diagnosis of premature CAD were not counted as recurrent events. Similarly, non-fatal ischemic events were not counted if they occurred within 30 days prior to death, and if two subsequent non-fatal ischemic events occurred within 30 days, only the first one was considered.

For the primary objective, the cumulative percentage of patients developing a first, second, and third recurrent ischemic event was estimated using the Kaplan-Meier method with follow-up censored at 10 years. The cumulative incidence of the first event type (treating other first events as competing risks) was also presented. The average rates of recurrence of the composite endpoint and individual components were calculated by fitting a loglinear Poisson model, and expressed as the number of new cardiovascular events divided by the number of patient-years of follow-up (number of events per 100 patient-years) with 95% confidence interval, for the overall population and stratified by sex. For the loglinear Poisson model, the outcome variable was the patient-level count of new cardiovascular events during follow-up. To adjust for differential follow-up, the model included an offset term equal to the logarithm of the years of follow-up for each patient. For estimating the event rate in the overall cohort, the model

included only an intercept parameter, which was estimated by maximum likelihood. The resulting point estimate and 95% confidence limits were exponentiated and multiplied by 100 to provide the estimated recurrence rate per 100 patient years. The third set of analyses assessed associations of pre-specified patient characteristics and risk factors evaluated at time of CAD diagnosis, with the rate of future ischemic event recurrence. These variables were age, sex, body mass index, ethnic group, chronic inflammation, cardiovascular risk factors, presentation, estimated glomerular filtration rate, LDL-C level, triglyceride levels, multivessel disease, treatment with statin at disarcharge and type of treatment (PCI or CABG). Cox proportional hazard regression models were used to assess associations with the rate of first recurrent event, and negative binomial loglinear regression was used for rate of multiple event recurrences. For the Cox proportional hazards models the outcome variable was the time to first MACE event recurrence. In patients without an event, time-to-event was censored at end of follow-up or 10 years if earlier. Associations with the predictor variables were expressed as hazard ratios for first MACE event recurrence. For the negative binomial loglinear regression the outcome variable was the count of the number of recurrent MACE events per patients. To adjust for differential follow-up, the model included an offset term equal to the logarithm of the years of follow-up for each patient. Associations with predictor variables were expressed as rate ratios for recurrent MACE events. For both multivariable regression models the variables included as independent variables were identified a priori based on clinical relevance.

Available data on risk factor prevalence (smoking, LDL-C ≥70 mg/dL) during follow-up were summarized by time post CAD diagnosis (0-1 year, 1-3 years, 3-5 years, and 5-10 years). Within each interval the number and percent of patients with smoking status, or with LDL-C ≥70 mg/dL, respectively, was summarized. We stratified the description of ongoing smoking according to baseline status (overall, never, former, current), and LDL-C elevation by whether baseline LDL-C was controlled (<70 mg/dL) or not. In patients without diabetes at baseline we

estimated the cumulative incidence of patients newly diagnosed with diabetes during 10 years of follow-up.

Descriptive statistics were calculated using observed data only. For regression models, missing data were imputed using a multiple imputation approach (n=25). No adjustment was made for multiple comparisons. All statistical analyses were performed using SAS software, Version 9.4, SAS Institute Inc. (Cary, NC, USA).

RESULTS

Baseline Characteristics

Out of 101,061 patients who presented to the Duke University Adult Cardiac Catheterization Laboratory between 1995 to 2013, 3655 (3.6%) patients aged less than 50 years had a first manifestation of obstructive coronary artery disease (**Supplemental Figure 1** shows study flow chart)**.** The median age of these individuals was 45 years [Interquartile Range 41 – 47], 27.5% of patients were women, 26.0% were African Americans and 6.5% presented before 35 years of age **(Table 1).** The main presentations were ST-segment elevation myocardial infarction (38.6%) and non-ST-segment elevation myocardial infarction (36.0%). The majority of patients had single vessel obstructive CAD (59.6%). Of interest, 9.5% of patients had kidney impairment with an estimated GFR < 60 mL/min, including 2.5% who required dialysis at baseline. Very few patients had a history of HIV, connective tissue disease, or malignancy.

Traditional Cardiovascular Risk Factors

Approximately 73% of individuals had at least two cardiovascular risk factors and 43% had 3 or more (Table 1). Active or prior smoking was the most frequent risk factor (60.8%), followed by hypertension (52.8%), family history of CAD (39.8%) and diabetes mellitus (23.8%). Obesity (Body Mass Index > 30 kg/m2) was prevalent in 47.1 % of this premature CAD population. Within 12 months of the index procedure, the median LDL-C was 117 [interquartile

range (IQR) 92 – 145] mg/dL, the median HDL-C was 37 mg/dL [IQR 31 – 34] and the median triglycerides were 141 mg/L [IQR 91 – 218]. Of note, the baseline LDL-C was >190 mg/ dL in 5.4% of patients and triglycerides ≥ 175 mg/ dL in 35.8 % of patients. When comparing age categories, individuals who presented very prematurely (≤ 35 years) were more frequently obese compared with the population between 35 to 45 years and above 45 years (53.2 % vs. 49.1 % vs. 44.2 %, $p<0.01$), and these individuals had a greater prevalence of LDL-C levels >190 mg/dL (11.2 % vs. 5.3 % vs. 4.7 %, $p<0.01$). The trend in cardiovascular risk factors at baseline is displayed in **supplemental table 1**: between 1995 and 2013, the rate of smokers and median LDL-C decreased among young patients with a first diagnosis of obstructive CAD. In contrast, the rate of diabetes and hypertension among young adults increased.

Table 1. Baseline characteristics stratified by age groups

	Overall (N=3655)	≤ 35 years (N=239)	>35 to ≤ 45 years (N=1772)	>45 to < 50 years (N=1644)	P-Value
Demographics					
Age (years)	45 (41, 47)	33 (30, 34)	42 (40, 44)	48 (47, 49)	
Female	1005 (27.5%)	55 (23.0%)	492 (27.8%)	458 (27.9%)	0.2749
BMI, median, (IQR)	30 (26, 34)	30 (27, 34)	30 (26, 34)	29 (26, 33)	0.0339
BMI>30 kg/m2	1714 (47.1%)	125 (53.2%)	866 (49.1%)	723 (44.2%)	0.0026
Race					0.2989
White	2376 (67.0%)	147 (63.9%)	1128 (65.6%)	1101 (68.9%)	
African American	921 (26.0%)	63 (27.4%)	460 (26.7%)	398 (24.9%)	
Native American	160 (4.5%)	13 (5.7%)	87 (5.1%)	60 (3.8%)	
Other	90 (2.5%)	7 (3.0%)	45 (2.6%)	38 (2.4%)	
Index Presentation					0.0016
STEMI	1410 (38.6%)	120 (50.2%)	687 (38.8%)	603 (36.7%)	
NSTEMI or unstable angina	1315 (36.0%)	76 (31.8%)	636 (35.9%)	603 (36.7%)	
Other	930 (25.4%)	43 (18.0%)	449 (25.3%)	438 (26.6%)	
Risk Factors, Comorbidity, Clinical History					
Smoking Status					0.0005
Never	1434 (39.2%)	103(43.1%)	699 (39.4%)	632 (38.4%)	
Former	417 (11.4%)	20 (8.4%)	168 (9.5%)	229 (13.9%)	
Current	1804 (49.4%)	116 (48.5%)	905 (51.1%)	783 (47.6%)	
Hypertension	1930 (52.8%)	90 (37.7%)	920 (51.9%)	920 (56.0%)	<.0001
Diabetes	871 (23.8%)	43 (18.0%)	415 (23.4%)	413 (25.1%)	0.0459
Family history of coronary artery disease	1456 (39.8%)	90 (37.7%)	719 (40.6%)	647 (39.4%)	0.5956
Hyperlipidemia	1696 (46.4%)	79 (33.1%)	850 (48.0%)	767 (46.7%)	<.0001
Number of Cardiovascular Risk Factors					
-- 0 risk factors	344 (9.4%)	37 (15.5%)	167 (9.4%)	140 (8.5%)	0.0026
-- at least 1	3311 (90.6%)	202 (84.5%)	1605 (90.6%)	1504 (91.5%)	0.0026
-- at least 2	2657 (72.7%)	145 (60.7%)	1299 (73.3%)	1213 (73.8%)	<.0001
-- 3 or more	1564 (42.8%)	71 (29.7%)	771 (43.5%)	722 (43.9%)	0.0001

Table 1 - suite	Overall (N=3655)	≤ 35 years (N=239)	>35 to ≤ 45 years (N=1772)	>45 to < 50 years (N=1644)	P-Value
Co-morbidities					
COPD	97 (2.7%)	4 (1.7%)	37 (2.1%)	56 (3.4%)	0.0353
Peripheral vascular disease	132 (3.6%)	3 (1.3%)	60 (3.4%)	69 (4.2%)	0.0581
Cerebrovascular disease	121 (3.3%)	4 (1.7%)	55 (3.1%)	62 (3.8%)	0.1894
Connective tissue disease	24 (0.7%)	3 (1.3%)	10 (0.6%)	11 (0.7%)	0.4611
Kidney disease	162 (4.4%)	8 (3.3%)	86 (4.9%)	68 (4.1%)	0.4177
Dialysis	93 (2.5%)	5 (2.1%)	53 (3.0%)	35 (2.1%)	0.2508
Liver disease	26 (0.7%)	0 (0.0%)	13 (0.7%)	13 (0.8%)	0.3923
HIV/AIDS	29 (0.8%)	0 (0.0%)	19 (1.1%)	10 (0.6%)	0.1121
History of Cancer	45 (1.2%)	1 (0.4%)	17 (1.0%)	27 (1.6%)	0.0973
History of ETOH	192 (5.3%)	16 (6.7%)	104 (5.9%)	72 (4.4%)	0.0876
Chronic Inflammatory disease	85 (2.3%)	4 (1.7%)	38 (2.1%)	43 (2.6%)	0.5190
Laboratory Results (median and IQR)					
LDL-C, mg/dL	117 (92, 145)	121 (95, 158)	117 (90, 145)	117 (92, 143)	0.0538
LDL-C 70-189 mg/dL	2642 (84.1%)	171 (79.9%)	1267 (84.1%)	1204 (84.7%)	0.2070
LDL-C ≥ 190 mg/dL	171 (5.4%)	24 (11.2%)	80 (5.3%)	67 (4.7%)	0.0005
HDL-C, mg/dL	37 (31, 44)	37 (30, 45)	36 (30, 44)	37 (31, 45)	0.0358
Triglycerides, mg/dL	141 (91, 218)	136 (91, 207)	141 (91, 223)	141 (90, 214)	0.6175
Triglycerides ≥ 175 mg/dL	1166 (35.8%)	69 (31.5%)	572 (36.6%)	525 (35.6%)	0.3245
Creatinine, (µmol/L)	1 (0.80, 1.10)	1 (0.80, 1.10)	1 (0.80, 1.10)	1 (0.80, 1.10)	0.2188
eGFR, (mL/min)	93 (79.5, 107.1)	101 (87.1, 116.6)	95 (81.2, 108.7)	89 (78.1, 103.2)	<.0001
eGFR<60 ml/min	342 (9.5%)	16 (6.8%)	152 (8.7%)	174 (10.8%)	0.0396
Genetic testing for HFH n= 632					
Patient had exome data in CATHGEN	632 (17.3%)	39 (16.3%)	311 (17.6%)	282 (17.2%)	0.8765
APOB pathogenic, likely pathogenic mutation	0 (0.0%)	0 0.0%)	0 (0.0%)	0 (0.0%)	
LDLR pathogenic, likely pathogenic mutation	4 (0.6%)	2 (5.1%)	2 (0.6%)	0 (0.0%)	0.0107
PCSK9 pathogenic, likely pathogenic mutation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Table 1 - suite	Overall (N=3655)	≤ 35 years (N=239)	>35 to ≤ 45 years (N=1772)	>45 to < 50 years (N=1644)	P-Value
Angiographic findings					
Number of Diseased Vessels					<.0001
1	2180 (59.6%)	171 (71.5%)	1084 (61.2%)	925 (56.3%)	
2	882 (24.1%)	43 (18.0%)	422 (23.8%)	417 (25.4%)	
3	593 (16.2%)	25 (10.5%)	266 (15.0%)	302 (18.4%)	
Left main ≥ 50%	191 (5.2%)	9 (3.8%)	81 (4.6%)	101 (6.1%)	0.0686
Left anterior descending ≥ 70%	2120 (58.0%)	133 (55.6%)	1038 (58.6%)	949 (57.7%)	0.6582
Left circumflex ≥ 70%	1473 (40.3%)	81 (33.9%)	702 (39.6%)	690 (42.0%)	0.0422
Right coronary artery ≥ 70%	1734 (47.4%)	87 (36.4%)	807 (45.5%)	840 (51.1%)	<.0001
Subsequent Treatment, within 30 days of cath					
PCI	2049 (56.1%)	135 (56.5%)	1003 (56.6%)	911 (55.4%)	0.7756
CABG	429 (11.7%)	28 (11.7%)	195 (11.0%)	206 (12.5%)	0.3835
PCI and CABG	34 (0.9%)	1 (0.4%)	20 (1.1%)	13 (0.8%)	0.4099
Medical Treatment only	1143 (31.3%)	75 (31.4%)	554 (31.3%)	514 (31.3%)	0.9993
Medications, within 30 days of Cath					
Statin	2577 (70.5%)	168 (70.3%)	1257 (70.9%)	1152 (70.1%)	0.8557
Aspirin	3455 (94.5%)	230 (96.2%)	1672 (94.4%)	1553 (94.5%)	0.4823
Blood pressure Medications	3432 (93.9%)	224 (93.7%)	1660 (93.7%)	1548 (94.2%)	0.8360
P2Y12 inhibitors	2484 (68.0%)	176 (73.6%)	1220 (68.8%)	1088 (66.2%)	0.0373
Beta Blockers	3191 (87.3%)	207 (86.6%)	1559 (88.0%)	1425 (86.7%)	0.4933
ACE inhibitors /ARB	2498 (68.3%)	173 (72.4%)	1203 (67.9%)	1122 (68.2%)	0.3715
Calcium Channel Blockers	652 (17.8%)	34 (14.2%)	299 (16.9%)	319 (19.4%)	0.0497
Diuretics	1874 (51.3%)	126 (52.7%)	891 (50.3%)	857 (52.1%)	0.5019

Footnote : BMI refers to body mass index ; IQR refers to interquartile range ; STEMI referes to ST-segment elevation myocardial infarction ; NSTEMI refers to non-ST segment elevation myocardial infarction ; HIV refers to human immunodeficiency virus ; AIDS refers to acquired immune deficiency syndrome ; ETOH refers to ethyl alcohol cunsomption; eGFR refers to estimated glomerular filtration rate; HFH refers to heterozygous familial hypercholesterolemia ; APOB refers to apolipoprotein B ; LDLR refers to LDL receptor, PCSK9 refers to Proprotein convertase subtilisin/kexin type 9 ; PCI refers to Percutaneous coronary intervention ; CABG refers to Coronary artery bypass graft ; ACE inhibitors refers to angiotensin-converting enzyme inhibitors ; ARB refers to angiotensin-receptor blocker

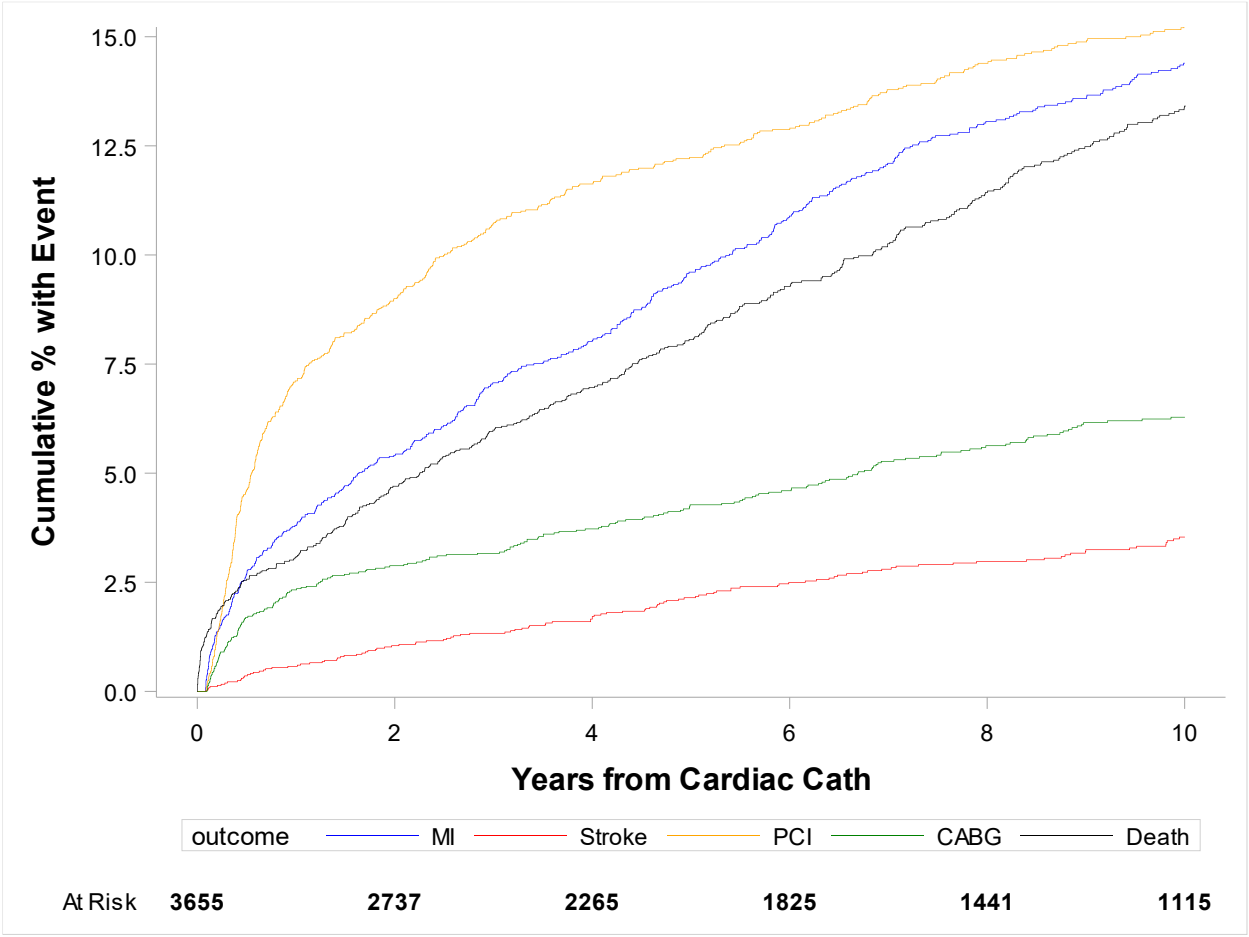
Prevalence of Heterozygous Familial Hypercholesterolemia

To ensure that premature CAD in this population was not due to monogenic disease, we evaluated the prevalence of familial hypercholesterolemia in a subset of our population. Of the 3655 patients in the present study, 632 (17.3%) had whole exome sequence data available. Only four of these patients were found to harbor pathogenic or likely pathogenic mutations, all within LDLR.

First Recurrent ischemic event

By 10 years, 52.9% of patients had developed at least one recurrent ischemic event defined by the composite of all-cause death, recurrent myocardial infarction, revascularization, or stroke. After premature CAD onset, the most frequent first events were follow-up revascularization PCI or CABG (15.3% and 6.3%), recurrent myocardial infarction (14.4%) or death (13.4%). Stroke was the first event in 3.5 % of patients **(Figure 1).**

Figure 1. Time to first subsequent MACE within 10 years after premature CAD diagnosis.



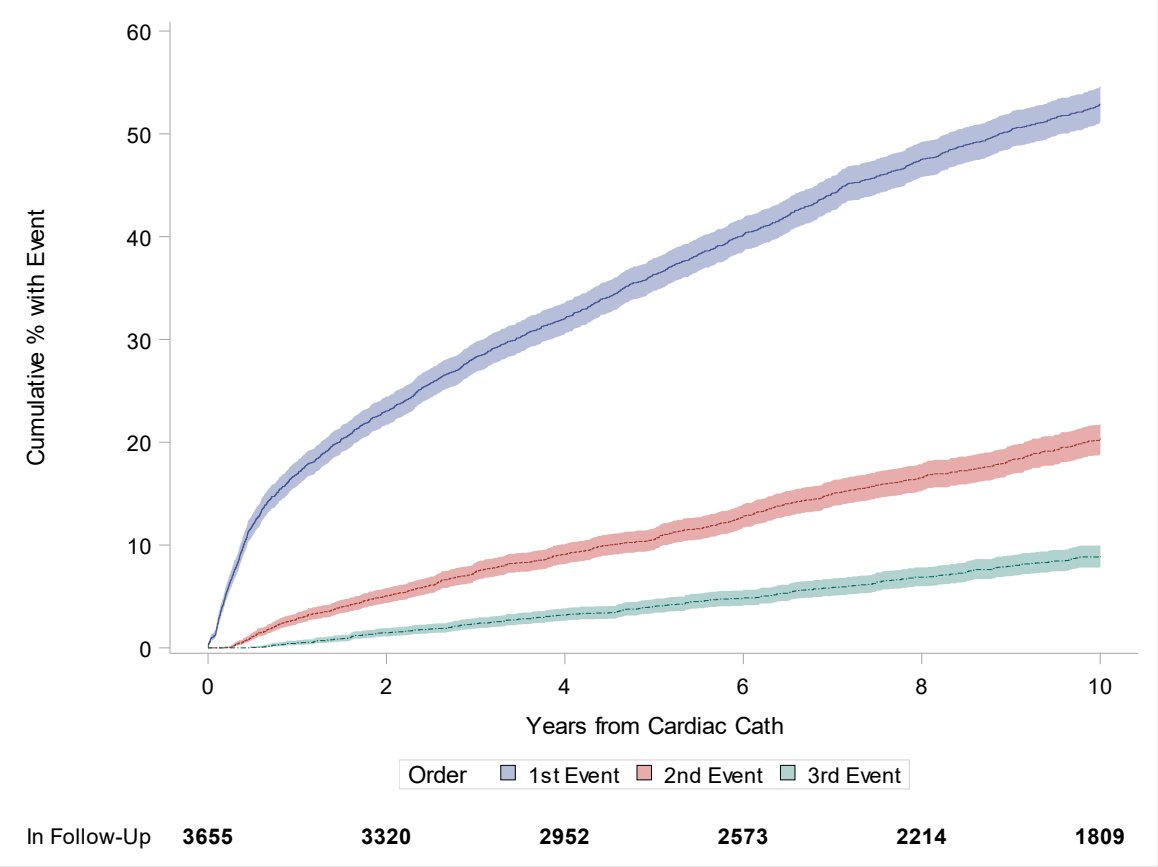
Footnote: MACE refers to major adverse cardiac events. CAD refers to coronary artery disease.

PCI refers to percutaneous coronary intervention. CABG refers to stable angina leading to coronary artery bypass graft. MI refers to myocardial infarction.

Multiple recurrent ischemic events

The time to first, second and third event is displayed in **Figure 2.** By 10 years, 18.6 % of patients had suffered a second event, and 7.9 % had suffered a third event. The all-cause mortality rate was 20.9% at 10 years. Overall, the present population experienced MACE at a rate of 10.0 (95% CI 9.6-10.4) events per 100 patient-years, with non-fatal myocardial infarction and death occurring at respective rates of 2.7 (95% CI 2.5-2.9) and 2.3 (95% CI 2.2-2.5) per 100 patient-years. Women and men had respective rates of major adverse cardio events of 12.2 (95% CI 11.4-13.0) and 9.2 (95% CI 8.8-9.6) per 100 patient-years.

Figure 2. Time to first, second or third MACE within 10 years after premature CAD diagnosis.



Footnote: MACE refers to major adverse cardiac events. CAD refers to coronary artery disease.

Factors associated with time to first recurrent ischemic event

The factors associated with subsequent events following premature CAD onset are displayed in **table 2**. Women with premature CAD were at a higher risk of a subsequent ischemic event compared with men (adjusted HR 1.15, 95% CI 1.03 – 1.28, p=0.01). Among traditional risk factors, baseline diabetes mellitus was the only variable independently associated with a first ischemic recurrence. Although infrequently observed, chronic inflammatory disease was strongly associated with a first ischemic recurrence (adjusted HR 1.61, 95% CI 1.23 – 2.11, p<.001). Baseline chronic kidney disease (estimated glomerular filtration rate below 60 ml/min), multivessel disease and absence of revascularization after a first event were also associated with poor outcomes.

Table 2. Factors associated with time to first ischemic recurrence

Covariate	Univariable Hazard Ratio with 95% CI	P-Value	Multivariable Hazard Ratio with 95% CI	P-Value
Age (per 10-year increase)	1.06 (0.96,1.16)	0.282	1.03 (0.93, 1.14)	0.565
Sex (Female v Male)	1.32 (1.20,1.47)	<.001	1.15 (1.03, 1.28)	0.010
BMI ≥ 27 (per 5 kg/m**2 increase)	1.06 (1.02,1.10)	0.002	1.04 (1.00, 1.09)	0.052
Ethnic group (white is the reference)		<.001		0.054
- Afro-American	1.29 (1.16,1.44)	.	1.10 (0.98, 1.23)	
- Native American & Other	1.16 (0.97,1.39)	.	1.16 (0.96, 1.39)	
Chronic Inflammation	1.69 (1.29,2.20)	<.001	1.61 (1.23, 2.11)	<.001
Family History of Coronary Disease	1.04 (0.95,1.15)	0.364	1.06 (0.96, 1.17)	0.213
Admission with ACS vs. no ACS	0.83 (0.75,0.93)	<.001	1.10 (0.99, 1.23)	0.080
Current/Former Smoker	0.96 (0.87,1.06)	0.431	1.03 (0.93, 1.13)	0.627
History of Hypertension	1.27 (1.15,1.39)	<.001	1.03 (0.93, 1.14)	0.521
Diabetes	1.68 (1.52,1.86)	<.001	1.35 (1.21, 1.51)	<.001
eGFR per 20 mL/min/1.73m^2 decrease	1.34 (1.28,1.40)	<.001	1.19 (1.13, 1.25)	<.001
LDL ≥ 120 per 20 mg/dL increase	0.97 (0.93,1.02)	0.280	1.02 (0.96, 1.08)	0.523
Triglycerides per 50 mg/dL increase	1.01 (0.99,1.04)	0.237	1.00 (0.98, 1.03)	0.909
Multivessel disease	1.39 (1.27,1.53)	<.001	1.47 (1.33, 1.63)	<.001
Statin at discharge	0.80 (0.72,0.88)	<.001	1.01 (0.91, 1.13)	0.823
Subsequent Treatment within 30 days		<.001		<.001
- PCI vs. Medical Treatment	0.41 (0.37,0.45)	.	0.45 (0.41, 0.50)	
- CABG vs. Medical Treatment	0.29 (0.24,0.34)	.	0.25 (0.21, 0.30)	

Footnote : BMI refers to body mass index ; ACS refers to acute coronary syndrome ; eGFR refers to estimated glomerular filtration rate; PCI refers to Percutaneous coronary intervention ; CABG refers to Coronary artery bypass graft ; ACE inhibitors refers to angiotensin-converting enzyme inhibitors ;

Factors associated with the rate of multiple recurrent events

The factors associated with the rate of multiple recurrent events are displayed in **table 3**. Baseline diabetes mellitus, kidney impairment and multivessel disease were associated with increased rates of multiple ischemic events. The absence of revascularization at the time of index diagnosis was also associated with the occurrence of multiple ischemic events.

Table 3. Factors associated with multiple ischemic recurrences

Covariate	Univariable Rate Ratio with 95% CI	P-Value	Multivariable Rate Ratio with 95% CI	P-Value
Age (per 10-year increase)	0.95 (0.65, 1.41)	0.817	0.88 (0.62, 1.25)	0.470
Sex (Female v Male)	1.45 (0.96, 2.17)	0.075	1.13 (0.77, 1.65)	0.535
BMI ≥ 27 (per 5 kg/m**2 increase)	1.07 (0.91,1.25)	0.410	1.05 (0.90, 1.22)	0.531
Ethnic group		0.175		0.512
- Afro-American	1.51 (0.98,2.34)		1.27 (0.85, 1.90)	
- Native American & Other	1.09 (0.52,2.30)		1.09 (0.56, 2.11)	
Chronic Inflammation	2.05 (0.59, 7.10)	0.255	1.87 (0.63, 5.52)	0.259
Family Hx of Coronary Disease	0.98 (0.67, 1.43)	0.904	1.05 (0.74, 1.48)	0.803
Admission with ACS vs. no ACS	0.82 (0.53, 1.26)	0.365	1.09 (0.73, 1.62)	0.673
Current/Former Smoker	0.90 (0.62, 1.33)	0.610	1.04 (0.72, 1.49)	0.842
History of Hypertension	1.47 (1.01, 2.14)	0.044	1.11 (0.77, 1.58)	0.581
Diabetes	1.99 (1.29, 3.06)	0.002	1.47 (0.99, 2.20)	0.058
eGFR per 20 mL/min/1.73m^2 decrease	1.48 (1.24,1.77)	<.001	1.29 (1.06, 1.55)	0.010
LDL ≥ 120 per 20 mg/dL increase	0.92 (0.77,1.10)	0.375	0.96 (0.80, 1.16)	0.677
Triglycerides per 50 mg/dL increase	1.01 (0.92,1.10)	0.875	1.00 (0.92, 1.09)	0.969
Multivessel disease	1.50 (1.03, 2.17)	0.034	1.44 (1.00, 2.06)	0.049
Statin at discharge	0.84 (0.57, 1.23)	0.365	1.01 (0.70, 1.48)	0.943
Treatment within 30 days		<.001		<.001
- PCI vs. Medical Treatment	0.42 (0.28, 0.61)		0.48 (0.33, 0.69)	
- CABG vs. Medical Treatment	0.30 (0.14, 0.61)		0.27 (0.14, 0.52)	

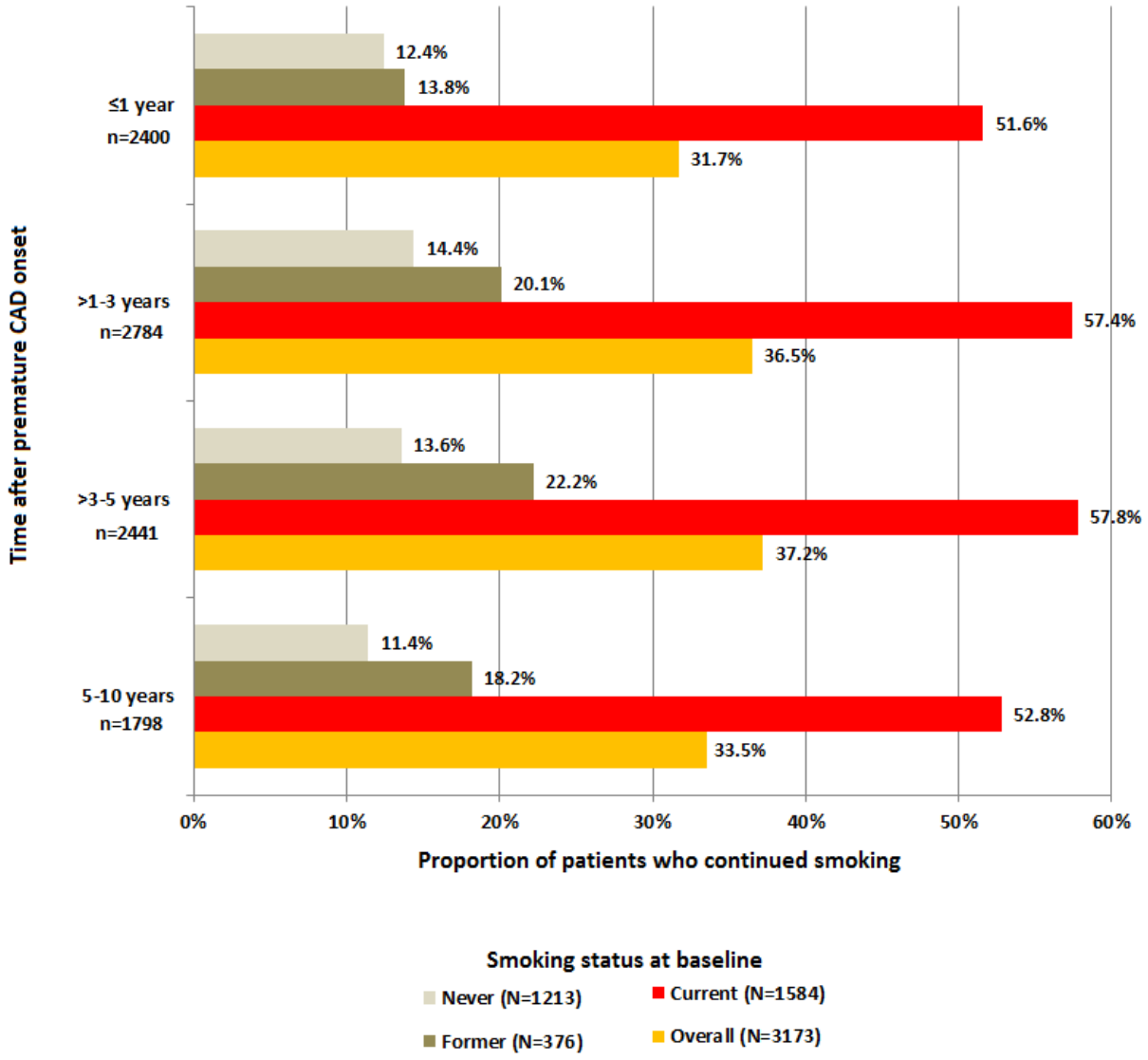
Footnote : BMI refers to body mass index ; ACS refers to acute coronary syndrome ; eGFR refers to estimated glomerular filtration rate; PCI refers to Percutaneous coronary intervention ; CABG refers to Coronary artery bypass graft ; ACE inhibitors refers to angiotensin-converting enzyme inhibitors

Evolution of cardiovascular risk factors after diagnosis of obstructive CAD

Across different time points of follow-up, 31.7 % to 37.2 % of patients continued smoking after premature CAD onset **(figure 3).** While most of these ongoing smokers were active smokers at baseline, more than 10% of patients who had never smoked before reported smoking during each interval assessed. LDL-C was rarely within latest guideline recommendation in this young population, with 89.3% of patients having LDL-C ≥ 70 mg/ dL during the first year after CAD diagnosis, and 84.3 % having at least one LDL-C value ≥ 70 mg / dL between 5-10 years after diagnosis**.** Only half of patients had a level of LDL-C within 100 mg/dL along follow-up **(Supplemental Figure 2 and Supplemental Table 2).** Eventually, the cumulative incidence of new onset diabetes mellitus in patients without history of diabetes mellitus at baseline was 16% (95 % CI 15% -18%) within 10 years after premature CAD onset **(Figure 4).**

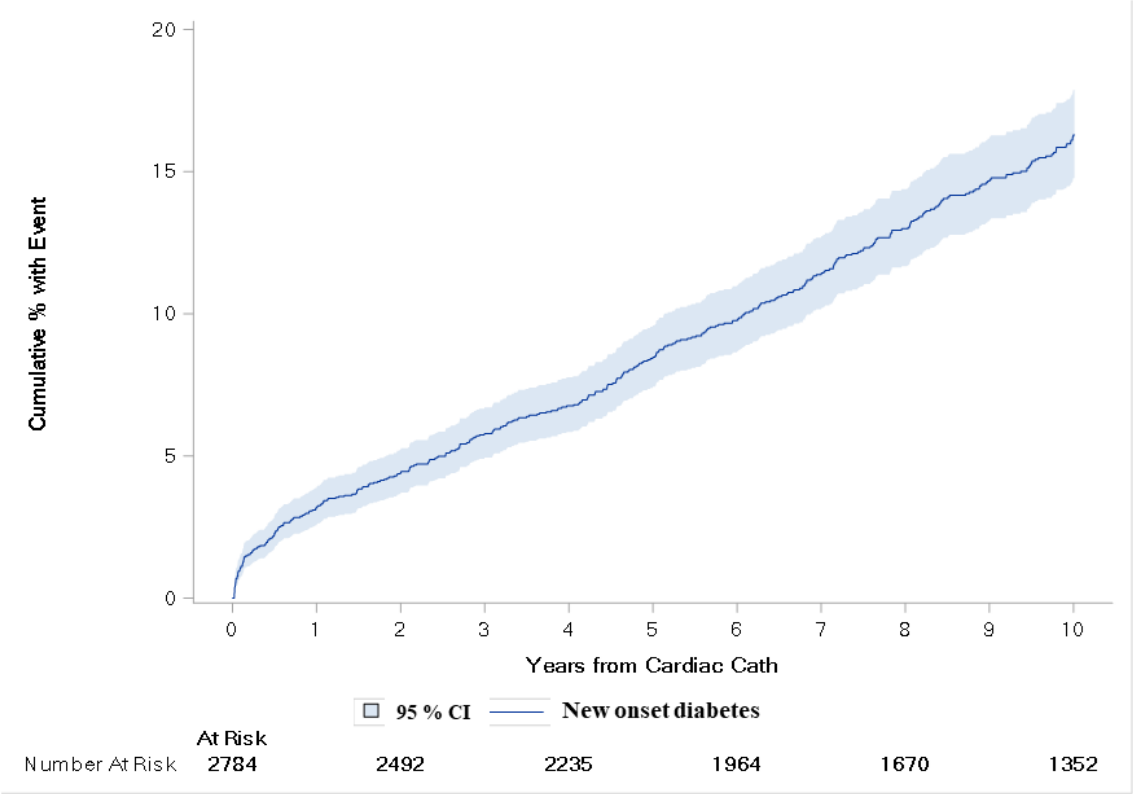
Figure 3. Smoking continuation after premature CAD diagnosis, stratified by baseline smoking status.

The n refers to the number of patients for whom smoking follow-up status was available.



Footnote : CAD refers to coronary artery disease

Figure 4. Cumulative rate of new onset diabetes after premature CAD diagnosis.



Footnote : CAD refers to coronary artery disease

DISCUSSION

In this analysis of Duke Databank for Cardiovascular Disease, there were multiple important findings. First, we observed that young patients with premature obstructive CAD often had numerous modifiable traditional cardiovascular risk factors. Second, premature CAD is a chronic evolving disease with half of patients experiencing a substantial evolution of coronary atherosclerosis within 10 years, and one out of 5 patients dying prematurely. Women, African American and Hispanic patients, and patients with diabetes mellitus or chronic inflammatory disease were at high risk of ischemic recurrences. Modification of cardiovascular risk factors over time was also poor in these young individuals as the rate of smoking remained high and LDL-C levels were above goal at follow up.

Our study showed that smoking was the most common risk factor amongst patients with premature CAD. Prior literature has shown that the accumulation of active smoking with an additional cardiovascular risk factor is frequent, and contributes to aggressive atherosclerosis and premature death (127). Nearly half of the study population were obese, compared with 10% to 30% in the US population reported between 2007-2014, suggesting the contribution of obesity as a risk enhancer for early atherosclerosis (128). Obesity predisposes patients to a metabolic syndrome such as insulin resistance and hypertriglyceridemia which is associated increased cardiovascular morbidity and mortality beyond traditional risk factors in middle aged individuals (129, 130). Of importance, the rate of diabetes in this young population with CAD was also elevated – and as frequent as what is usually observed in an average CAD population in the US. This comes in contrast with findings from a prospective cohort of French individuals with premature CAD, for whom obesity and diabetes were rare, but active smoking and high LDL-C levels were much more frequent (121). Overall, the present study supports the notion that there are several modifiable risk factors in individuals with premature CAD. Furthermore, our findings emphasize the importance of early intervention either through pharmacologic treatments to aid

in smoking cessation and reducing LDL-C, as well as lifestyle modifications for weight loss and a healthy diet (131–133).

Conversely, non-modifiable risk factors were not as apparent in our findings compared to modifiable ones – as genetic mutations related to HeFH were found in 1 % of the subset of tested individuals. There were 5% of individuals with baseline LDL-C above 190 mg/dl ; this proportion increased to 11% in patients who presented with CAD before 35 years. Previous reports have shown a proportion of up to 20% of HeFH among young adults with myocardial infarctions (50). One explanation could be that only 17% of our study population had genetic testing and complete family history information was not readily available to calculate a Dutch Lipid Score. Finally, chronic diseases responsible for clinical or subclinical inflammation such as HIV, cancer or connective tissue diseases are present in a small proportion of patients, but significantly contribute to poor outcomes. Such findings highlight the potential benefits of innovative anti-inflammatory therapies to prevent cardiovascular events in certain subgroups of patients with premature CAD (120, 134).

One out of five patients with premature CAD died within 10 years of follow-up. These young individuals were also found to have multiple recurrences of events, especially atherosclerotic progression leading to stable angina or recurrent myocardial infarctions. With almost 10 events per 100 patient-years, including recurrent myocardial infarction or death, patients with premature CAD display worse outcomes than those reported in patients over 50 years of age, even including higher risk groups (74, 98) . Such a pejorative prognosis highlights the needs for more aggressive primary and secondary prevention, with appropriate smoking cessation strategies and low LDL-C target goals in young patients at risk. Of importance, more than half of patients continued smoking despite early CAD ; this observation is consistent with the findings of the Partners YOUNG-MI registry, which displayed a clear association with subsequent mortality (135). This also demonstrates the need for specific trials to test innovative

strategies like early PCSK9 inhibitors as soon as premature CAD is diagnosed, for these individuals with a life-long atherosclerotic burden. Attention should also be given to risk enhancers such as biomarkers like lipoprotein (a) which are hereditary and can also lead to premature cardiovascular disease (136, 137). Extended DAPT duration is another path requiring evaluation, in this population with a low bleeding risk with early recurrent ischemic events. The other unmet need is a specific consideration of these individuals in scientific guidelines, to provide a specific cardiovascular risk assessment and to guide intensive therapies for which they are currently rarely eligible (109, 138, 139). In a recent evaluation of the recent 2018 ACC/AHA Blood Cholesterol guidelines in DDCD, we found that less than 50 % of patients admitted for a first MI before the age of 55 years-old would have been eligible for a primary prevention statins prior to this event – in comparison with 75 to 85 % of older MI patients (140). The major explanation is the importance contribution of age in the risk stratification by the 10-year ASCVD risk score (141).

Our findings also show that women with premature CAD have higher rates of ischemic recurrences, including all-cause death and myocardial infarction when compared with men with premature CAD. These sex-specific findings for prognosis have been reported across a broad spectrum of cardiovascular diseases and have been mostly associated with less-than-optimal secondary prevention and absence of intensive therapy (142, 143). The failure to provide adequate prevention strategies in women has been attributed to the misconception that they do not exhibit classic signs of atherothrombosis (144). The present study demonstrates that the proportion of women with premature atherosclerotic CAD is high, as they represent more than one out of four patients of the cohort. African Americans and Hispanics also display a higher risk of recurrences than Caucasians. Socioeconomic factors, absence of tailored secondary prevention and less access to healthcare and subsequent prevention strategies have been reported

as factors contributing to disparate outcomes according to differences in sex, race, and ethnicity (145).

The control of cardiovascular risk factors was suboptimal during follow-up in our study, in a population for whom life expectancy in the United States should exceed 30 years. While great advancements have been made in the contribution of genetic polymorphisms and gene-scores to risk stratify early onset of CAD and its poor prognosis (146, 147), the present observations display a clear need to improve strategies aimed at modifiable cardiovascular risk factors. This effort is paramount, as genetic predispositions and environment factors frequently overlap and carry a combined high risk burden on cardiovascular outcomes (148). The efforts to promote a healthy lifestyle in young patients can only be successful via multimodal and multifactorial interventions involving long-term social, psychological and medical assessment. New strategies are needed to promote primary and secondary prevention in this young and active population.

LIMITATIONS

We acknowledge several limits of this observational study. This is a single-center study with a population referred to a quaternary care hospital. We included subsequent PCI or CABG as a clinical endpoint; while the performance of PCI and CABG can be subjective, these are meaningful events related to the progression of atherosclerosis requiring interventional treatments and are important to the broad patient population. The events that occurred outside of Duke hospital were patient-reported, suggesting a possible underestimation of the rate of events. There was only a little proportion of patients for whom genetic data were reported. The important difference between the proportion of mutations and HFH according to Dutch Lipid Score warrants further investigations. The associations displayed in the multivariable models should be interpreted as hypothesis generating, because of the potential for confounding and unmeasured bias. For instance, the compliance to medication, blood pressure control, recovery

of left ventricular fraction and possible social and psychological bias were not measured or collected for the model (149, 150). Furthermore, the model could not evaluate how risk factor changes during follow-up might relate to outcomes, because of the heterogeneity in the collection and completeness of data in time.

CONCLUSIONS

Premature CAD is an aggressive disease with a high rate of ischemic recurrences and premature death. Younger individuals have a high proportion of modifiable cardiovascular risk factors, with suboptimal control of smoking and LDL-C cholesterol over time being frequent. This highlights the need to implement early, multimodal, and innovative prevention strategies for younger patients in both primary and secondary prevention.

CLINICAL PERSPECTIVES

What is new?

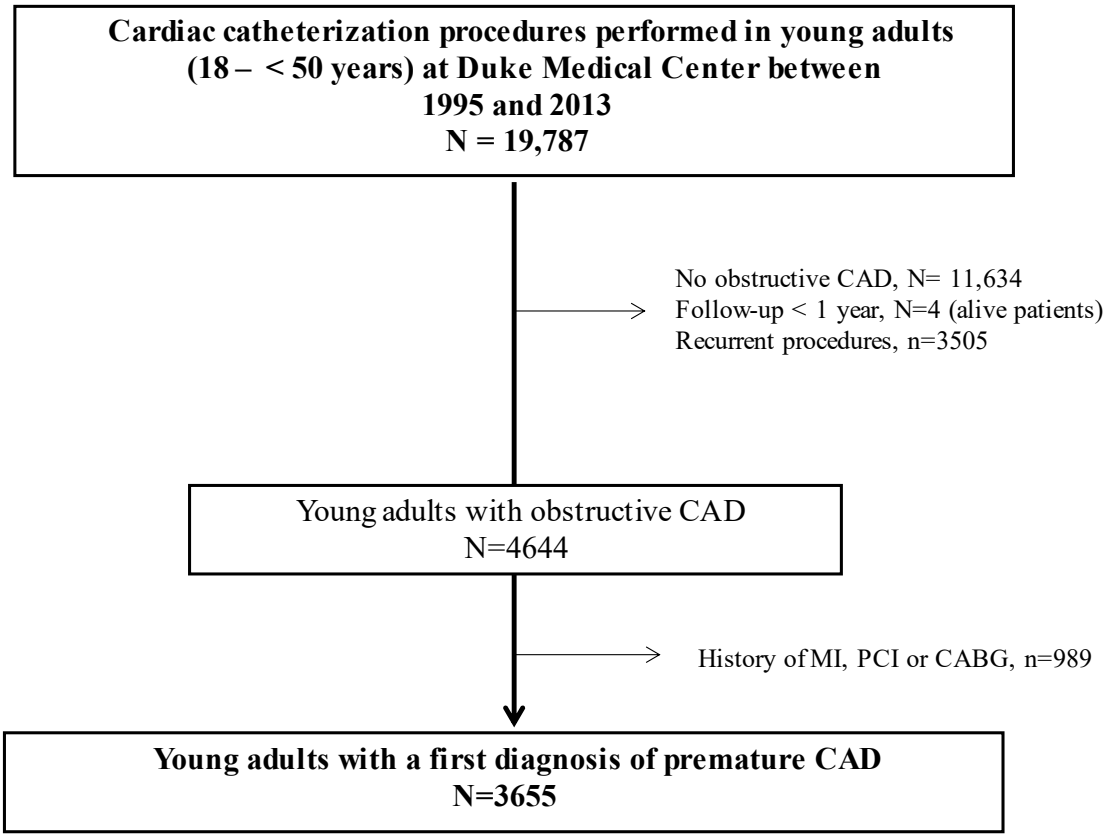
- Patients with premature coronary artery disease have a high rate of concomitant modifiable cardiovascular risk factors.
- Premature coronary artery disease is a fast-evolving disease with a high rate of major adverse cardiac events and a 10-yeart mortality of 21 %.
- Factors of subsequent ischemic event were: female sex, diabetes, chronic inflammatory disease, chronic kidney disease and absence of revascularization.
- Around one third of patients with premature CAD continued smoking, more than 80 % had LDL-C above target goals and 16 % of patients developed diabetes.
- Less than 1 % of patients had mutations associated with heterozygous familial hypercholesterolemia in the subset of patients with genetic data.

What are the clinical implications?

- Education should be provided to young individuals with several cardiovascular risk factors regarding their risk of developing CAD, and the long-term prognostic of premature CAD.
- Specific primary prevention strategies targeting active smoking, lifestine and statins should be provided to young patients with several concomitant risk factors.
- Long-term secondary prevention strategies should be provided to young patients with early CAD, including cessation of smoking, high-intensitiy lipid-lowering therapy and extended dual antiplatelet therapy.
- A specific attention should be brought to the high risk of developing diabetes in this young population.
- More research is needed to improve care in woman with premature CAD, as they are at higher risk to develop subsequent ischemic events than men.

SUPPLEMENTAL MATERIAL

Supplemental figure 1. Study flow-chart

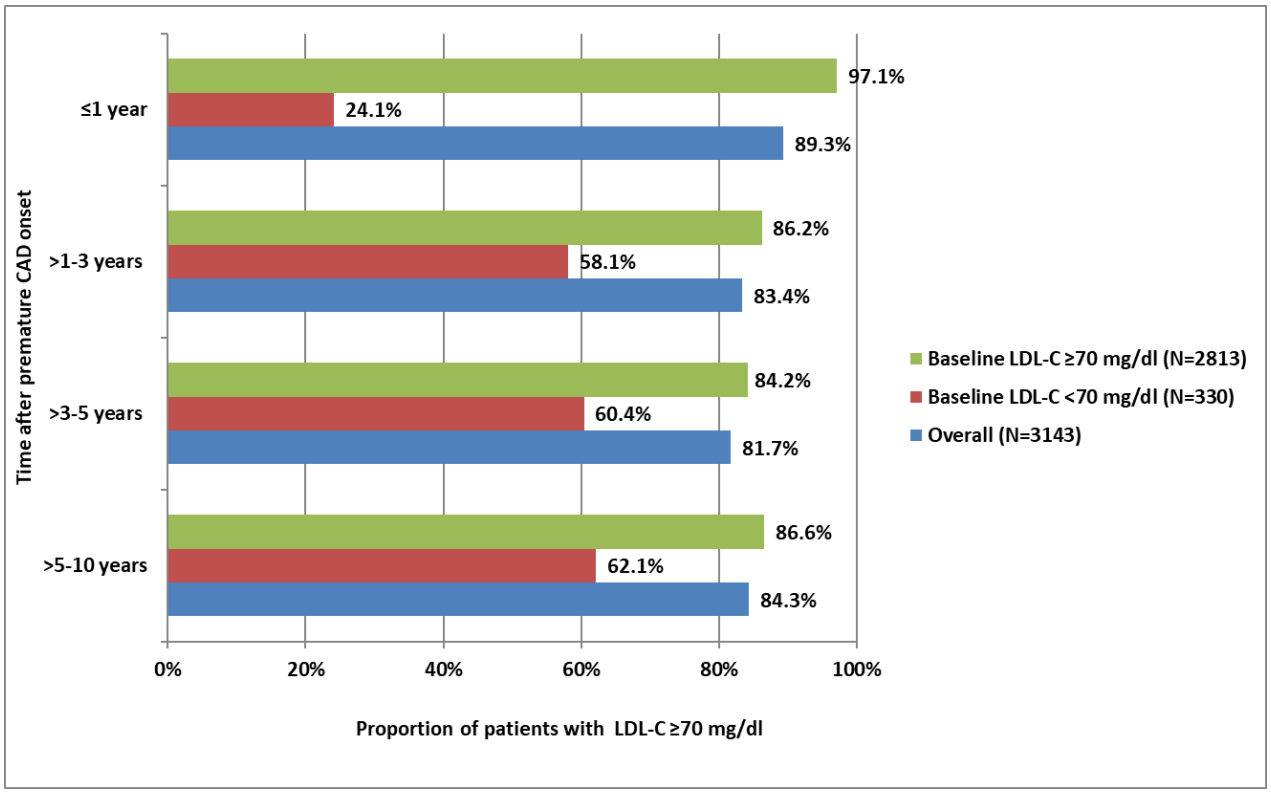


Supplemental table 1: Trend in cardiovascular risk factors in young patients admitted with a first diagnosis of obstructive CAD

	Year of inclusion in DDCD				
	1995-1999 (N=1303)	**2000-2004 (N=1134)**	**2005-2009 (N=768)**	**2010-2013 (N=450)**	**P-Value for Trend**
Baseline Risk Factor					
Current smoking	728 (55.9%)	603 (53.2%)	307 (40.0%)	166 (36.9%)	<.0001
Hx of diabetes	304 (23.3%)	275 (24.3%)	171 (22.3%)	121 (26.9%)	0.4039
Hx of hypertension	641 (49.2%)	620 (54.7%)	407 (53.0%)	262 (58.2%)	0.0017
Hx of hyperlipidemia	668 (51.3%)	524 (46.2%)	302 (39.3%)	202 (44.9%)	<.0001
LDL-C (median, interquartile ranges)	125 (98, 150)	114 (90, 142)	114 (86, 142)	113 (85, 139)	<.0001

Trend P-values from Cochran-Armitage test (discrete variables), test of Spearman correlation (continuous variables)

Supplemental figure 2. Proportion of patients with follow-up LDL-C within guideline recommendation (<70 mg/dL) after premature CAD onset according to baseline LDL-C. The n refers to the number of patients for whom LDL-C follow-up status was available



Supplemental table 2. Proportion of patients with follow-up LDL-C within <100 mg/dL) after premature CAD onset according to baseline LDL-C. The n refers to the number of patients for whom LDL-C follow-up status was available.

		Baseline	
	Overall (N=3143)	**LDL<100 mg/dL (N=1019)**	**Baseline LDL ≥ 100 mg/dL (N=2124)**
Cath Date to <=1 year	1938/2934 (66.1%)	115/958 (12.0%)	1823/1976 (92.3%)
>1-3 years post-cath	565/1069 (52.9%)	116/334 (34.7%)	449/735 (61.1%)
>3-5 years post-cath	437/865 (50.5%)	90/265 (34.0%)	347/600 (57.8%)
>5-10 years post-cath	522/978 (53.4%)	110/293 (37.5%)	412/685 (60.1%)

3.GlycA is a biomarker for premature coronary artery disease and events in patients with stable outpatient chest pain: a PROMISE trial substudy

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ABSTRACT

BACKGROUND. GlycA is a measure of glycosylated proteins and has emerged as a novel biomarker of chronic subacute inflammation and thus may serve as a biomarker for premature cardiovascular disease.

AIM. To determine if GlycA levels are associated with prevalent obstructive coronary artery disease (oCAD) and incident cardiovascular events and, and to evaluate for interactions by age for premature CAD.

METHODS. NMR spectroscopy was used to determine GlycA levels in frozen, stored plasma from 4019 participants with available biospecimens enrolled in the PROMISE trial. Univariate and multivariable logistic regression was used to determine association of GlycA levels with prevalent oCAD (stenosis ≥ 70%) in a subset of 1,789 participants randomized to cardiac computed tomography angiogram (CTA, core-lab adjudicated). Cox proportional hazards was used to determine association of GlycA levels with a time-to-incident cardiovascular (CV) events (composite of death, myocardial infarction, or unstable angina) and death. Analyses were stratified by age groups (premature [< 55 yo; n=515], early [55 – 65 yo; n=808] and average-age CAD [>65 yo; n= 475]) and interaction terms with age included in models for CAD and incident events.

RESULTS. Individuals in the highest GlycA quartile were more frequently smokers and had a greater prevalence of diabetes, hypertension and metabolic syndrome than those in the lowest quartile. GlycA levels were associated with oCAD (adj OR per 1 SD, 1.34, 95% CI [1.12 - 1.60], p<0.01) and remained significant even after adjustment for high sensitivity C-reactive protein (hs-CRP). During a median follow-up of 2.01 years (IQR 1.44 – 2.70), GlycA levels were associated with incident CV events (adj HR 1.29 per 1 SD, 95% CI, [1.10 - 1.51], p<0.01), and death (adj HR 1.56 (per 1 SD) [1.27 - 1.92], p<0.01). In analyses stratified by age groups, GlycA levels were significantly associated with CAD and incident events only in the premature group, and showed greater improvements in discrimination in this group.

CONCLUSIONS. In stable symptomatic outpatients without known CAD being evaluated for suspected CAD, higher levels of GlycA were independently associated with increased prevalence of oCAD and incident CV events in the premature age group, even after adjustment for hsCRP. Further, GlycA improved discrimination of CAD and events in this age-group. These results highlight the potential role of GlycA as a biomarker for premature CAD and incident events in young patients.

ABBREVIATIONS

CAD: Coronary artery disease

NMR: Nuclear Magnetic Resonance

oCAD: obstructive CAD

CRP: C-reactive protein

CTA: Computed Tomographic Angiography

OR: Odds Ratio

HR: Hazard Ratio

INTRODUCTION

Inflammation is a major component in the pathophysiology of atherosclerosis and coronary artery disease (CAD) and a potential therapeutic target for reducing cardiovascular morbidity (54, 151). Nonetheless, the attributable contribution of inflammation across the different presentations of CAD and subgroups of patients is not well described. Further, the role of biomarkers for different molecular components of inflammation is under investigation. Recent studies have demonstrated that chronic inflammatory diseases are a contributor to the development of premature CAD and a are associated with recurrent ischemic events and poor outcomes (51, 152). Precise understanding of the contribution of inflammation in accelerated atherosclerosis on top of other traditional risk factors is paramount to tailor primary and secondary prevention therapies but requires adequate biomarkers.

Recently, a novel inflammatory biomarker, GlycA, has been described as a composite signal of the glycosylation of acute phase proteins during inflammation. GlycA is measured by proton nuclear magnetic resonance (NMR) and spectroscopy, and is an integrated measure of glycosylation of acute phase inflammatory proteins and cytokines(80, 153, 154). GlycA is a long-term and stable marker of sub-clinical inflammation and tissue damage, with a good predictive value of adverse events in apparently healthy patients without medical history (155). GlycA is a correlate of cardiovascular risk factors in healthy patients, cardiovascular events in patients with ischemic heart disease, disease activity, and severity in patients with auto-immune pathologies (156–160). These associations were observed in models also including CRP, highlighting GlycA to report other aspects and pathways of inflammation(161, 162).

Thus, using data from the PROMISE trial and GlycA levels as a surrogate for chronic sub-clinical inflammation, we aimed to 1) evaluate the association between GlycA and a first diagnosis of obstructive CAD (oCAD) in outpatients with angina; 2) evaluate the association

between GlycA and cardiovascular outcomes; 3) determine the role of GlycA as a biomarker in premature CAD and CV events by evaluating interactions with age.

METHODS

Study design and population

The present study is a biomarker sub-analysis of the PROMISE trial with available biospecimens. The study of biomarkers was pre-specified in the PROMISE trial protocol. The design and results of the PROMISE multicenter randomized trial have been previously published (75, 76). Briefly, study participants (n=10,003) were outpatients with stable angina but without history of cardiac disease, requiring a non-invasive cardiovascular testing for further evaluation. Participants were randomly assigned to coronary computed tomographic angiography (CTA) versus functional testing. Enrollment began on July 27, 2010 and was completed on September 19, 2013. Follow-up visits were performed at 60 days at the study sites and centrally by means of telephone or mail at 6-month intervals after randomization. Over a median follow-up of 25 months, there was no difference in the composite primary endpoint of death, myocardial infarction, hospitalization for unstable angina or major procedural complication, between the CTA group and the functional testing group.

GlycA measurement

NMR spectroscopy was used to quantify GlycA levels in frozen, stored plasma from 4019 participants enrolled in the biomarker substudy of the parent PROMISE trial at LipoScience, Inc., using the LipoProfile-4 algorithm from NMR spectra obtained from the automated NMR Profiler system as described previously (156–160). The GlycA NMR signal emerges from the glycosylation of side-chains of mainly five acute phase proteins: orosomucoid, α1-antitrypsin, α1-antichymotrypsin, haptoglobin and transferrin (80, 81).

Study endpoints

The presence of oCAD was determined in a subset of the study population randomized to the CTA arm (n=1,798) using a CT core lab (Massachusetts General Hospital) and was defined as a coronary stenosis ≥ 70 % in a primary epicardial coronary artery or a stenosis ≥ 50 % in the left main artery. Level III-certified readers in the core lab were blinded to demographic and clinical data and with good inter-reader variability (163).

Cardiovascular events were defined as the composite of all-cause death, myocardial infarction, or unstable angina. Myocardial infarction was defined as an elevation of cardiac biomarker and a clinical or electric sign of ischemia or infarction (75, 76). Unstable angina requiring hospitalization was defined as angina or other ischemic symptoms ≥ 10 minutes and electric or angiographic signs of ischemia requiring hospitalization for 48 hours. All events were centrally adjudicated as part of the parent PROMISE clinical trial.

Because of an *a priori* interest in the role of biomarkers for premature CAD, three age of CAD diagnosis subgroups were defined based on age at enrollment in the PROMISE trial in individuals found to have oCAD on CT: premature CAD (<55 years old), early CAD (55-65 years old) and average-age CAD (> 65 years old).

Statistical analysis

Descriptive statistics are presented as mean and standard deviation for continuous variables and frequencies and percentages of patients for categorical variables. Baseline characteristics are presented stratified by quartiles of untransformed GlycA levels and compared; ANOVA was used to compare characteristics across quartiles for continuous variables or a chi-square test for categorical variables. For subsequent analyses, GlycA values were transformed into a standardized Z-score (where units represent 1 standard deviation [SD]) and analyzed as a continuous variable.

Univariate and multivariable (adjusted for age, sex, diabetes, hypertension, and current smoking) logistic regression was used to determine the association between GlycA and oCAD in the CTA group (n=1,798). A sensitivity analysis including high sensitivity CRP (hsCRP) in the model predicting oCAD was performed. To evaluate the statistical performance of models involving GlycA for discriminating oCAD, we calculated the AUCs of models for (1) clinical cardiovascular risk factors; (2) clinical cardiovascular risk factors and Diamond Forrester score; and (3) clinical cardiovascular risk factors and GlycA levels(164). For incident event analyses, univariate and multivariable Cox proportional hazards regression models with the same covariates were used to evaluate the association between GlycA and time-to-cardiovascular events and time-to-death in the overall population with GlycA measurements (n=4,019).

For each of these analyses, to determine association with premature CAD and differences across age-categories, analyses stratified by age-group were conducted (excluding age as covariate) and estimates across age-groups visually compared. All P-values are 2-sided and were considered significant if <0.05. All analyses were performed using the R foundation for statistical computing, Vienna, Austria. All individuals consented to the parent PROMISE clinical trial and the biomarker substudy and the Duke Institutional Review Board (IRB) approved the study.

RESULTS

Baseline characteristics

The baseline characteristics of the study population (n=4,019) stratified by quartiles of GlycA are presented in **Table 1**. The prevalence of cardiovascular risk factors was higher in increasing quartiles of GlycA. Individuals in the highest quartile (Q4) of GlycA were more likely to be black, (Q4: 12.2 % vs. Q1: 8.2 %, p<0.001) with a higher body mass index (BMI: Q4: 32.6 vs Q1: 28.9 p<0.001) and have a sedentary lifestyle (Q4: 57.8 % vs. Q1: 36.4% p<0.001) as compared with the lowest quartile (Q1). They also had a higher prevalence of hypertension (Q4: 73.8% vs. Q1: 55.7%, p<0.001), history of smoking (Q4: 56.2% vs. Q4: 44.7%, p<0.001), and had two times the prevalence of diabetes (Q4: 33.5% vs. Q1: 12.8%) and metabolic syndrome (Q4: 53.3 % vs. Q1: 26.5%) as individuals in Q1.

Table 1. Baseline characteristics of the study population stratified by quartiles of GlycA

	Overall Study Population	GlycA Quartile				P-value
		1	2	3	4	
Number of participants	**4,019**	**1,015**	**1,007**	**999**	**998**	
Mean age – yr ± SD	60.5 ± 8.1	60.7 ± 8.1	60.5 ± 8.0	60.7 ± 8.6	60.1 ± 7.8	0.2
Female sex (%)	53.3 %	41.3 %	47.9 %	56.7 %	67.8 %	<0.001
Racial group (%)						<0.001
White	88.2 %	88.2 %	89.9 %	88.6 %	86.0 %	
Black	8.9 %	8.2 %	6.9 %	8.2 %	12.2 %	
Other	2.9 %	3.6 %	3.2 %	3.1 %	1.8 %	
Mean body-mass index ± SD	30.8 ± 6.2	28.9 ± 5.3	30.1 ± 5.6	31.5 ± 6.2	32.6 ± 6.9	<0.001
Cardiovascular risk factors						
Hypertension (%)	65.4 %	55.7 %	63.1 %	69.2 %	73.8 %	<0.001
Diabetes (%)	21.9 %	12.8 %	17.9 %	23.7 %	33.5 %	<0.001
Dyslipidemia (%)	67.4 %	63.9 %	67.3 %	70.9 %	67.3 %	0.01
Family history of premature CAD (%)	32.5 %	32.0 %	31.2 %	32.8 %	34.2 %	0.5
Current or past tobacco use (%)	51.1 %	44.7 %	50.3 %	53.4 %	56.2 %	<0.001
Metabolic syndrome (%)	38.8 %	26.5 %	32.3 %	43.2 %	53.3 %	<0.001
No risk factors	2.7 %	4.6 %	3.3 %	1.7 %	1.0 %	<0.001
Mean no. of risk factors per patient	2.4 ± 1.1	2.1 ± 1.0	2.3 ± 1.1	2.5 ± 1.1	2.6 ± 1.1	<0.001
Mean combined Diamond and Forrester and Coronary Artery Surgery Study risk score	53.9 ± 21.2	56.3 ± 21.0	54.9 ± 21.4	53.6 ± 20.8	50.6 ± 21.2	<0.001
Co-morbidities						
Peripheral arterial or cerebrovascular disease	5.9 %	4.7 %	5.1 %	6.3 %	7.6 %	0.03
CAD risk equivalent	26.0 %	16.6 %	21.4 %	28.4 %	37.9 %	<0.001
Sedentary lifestyle	46.7 %	36.4 %	42.2 %	50.7 %	57.8 %	<0.001
Primary presenting symptom						
Chest Pain	71.4 %	72.8 %	73.1 %	69.5 %	70.1 %	
Dyspnea on exertion	16.1 %	14.7 %	14.8 %	16.9 %	18.1 %	0.2
Other	12.5 %	12.5 %	12.1 %	13.6 %	11.7 %	
Type of angina						
Typical	12.6 %	11.8 %	12.2 %	13.7 %	12.7 %	
Atypical	78.7 %	78.4 %	78.7 %	78.0 %	79.5 %	0.6
Nonanginal pain	8.7 %	9.8 %	9.0 %	8.3 %	7.8 %	

Association between GlycA with oCAD

All PROMISE participants were not known to previously have CAD. In the 1,798 study subjects in the biomarker sub study randomized to the CTA group, N=118 (6.6%) were found to have oCAD. In univariate analyses, GlycA levels were associated with oCAD disease (OR 1.28, 95% CI [1.08 - 1.52], p=0.004), and remained significant even after adjustment with pre-specified covariates (aOR 1.34, 95% CI [1.12 - 1.60], p=0.002). In sensitivity analyses adding hs-CRP to the model, the association between GlycA and oCAD remained significant (aOR 1.30, 95% CI [1.03 – 1.63]. The addition of GlycA to multivariable models on top of clinical cardiovascular risk factors demonstrated that GlycA improved discrimination of oCAD (AUC 0.73) than models involving the Diamond Forrester score (AUC 0.71) or for clinical cardiovascular risk factors alone (AUC 0.71) (**Table 2**). GlycA especially improved the AUC for patients with oCAD before the age of 55 years-old **(figure 1).**

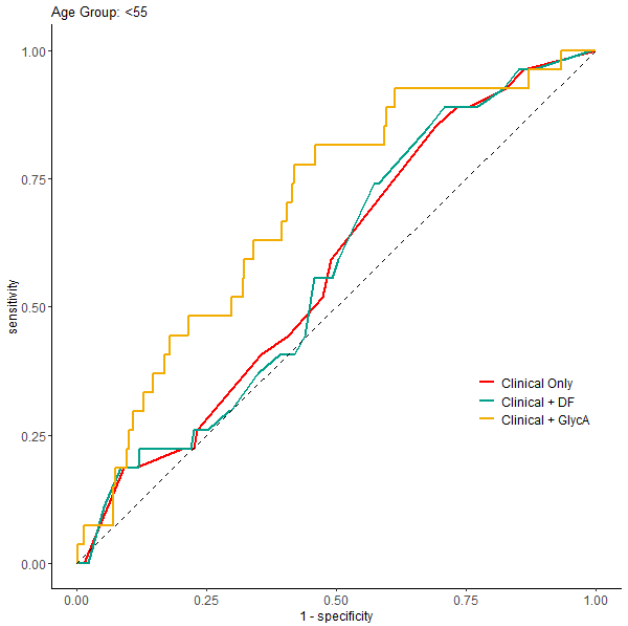
Table 2. AUC of multivariable models for discriminating oCAD according to age.

Age Group	Clinical Only	Clinical + Diamond Forrester Score	Clinical + GlycA
All	0.71	0.71	0.73
<55	0.58	0.58	0.69
55-65	0.76	0.78	0.77
>65	0.68	0.68	0.72

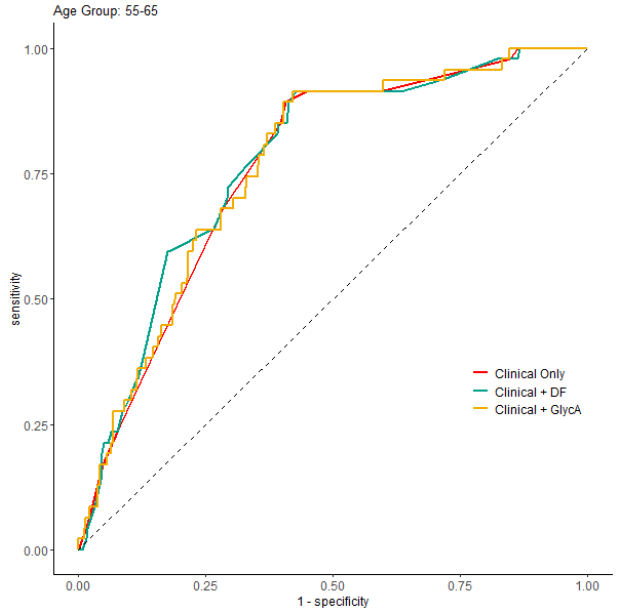
AUC refers to area under the curve.

Figure 1. AUC of multivariable models for discriminating oCAD according to age

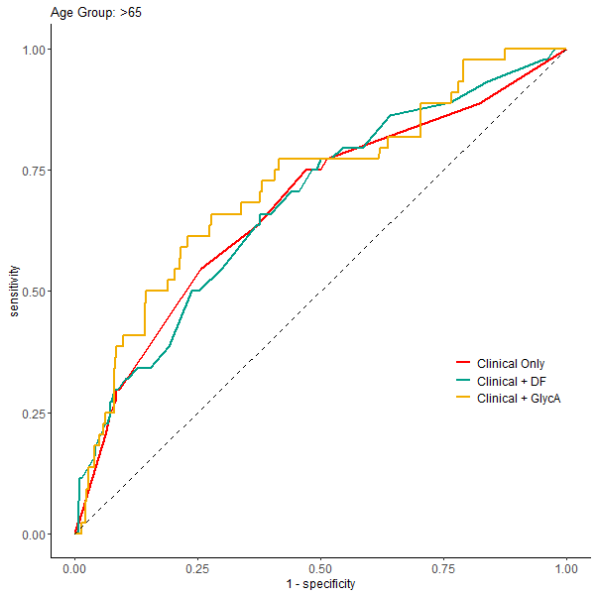
Age < 55 years



Age 55 – 65 years



Age > 65 years



Clinical

Clinical + Diamond Forrester Score

Clinical + GlycA

GlycA, age and premature CAD

We had a prespecified interest to understand the potential role of GlycA as a biomarker in premature CAD and to evaluate the association of GlycA by age. The AUC for the clinical cardiovascular risk factor model and the clinical plus Diamond-Forrester model was the least discriminative for oCAD in the premature CAD group. Furthermore, the AUC increase for oCAD was higher in patients aged < 55 years (0.11) than in patients aged 55 – 65 years (0.01) or > 65 years (0.04) (**Table 2**).

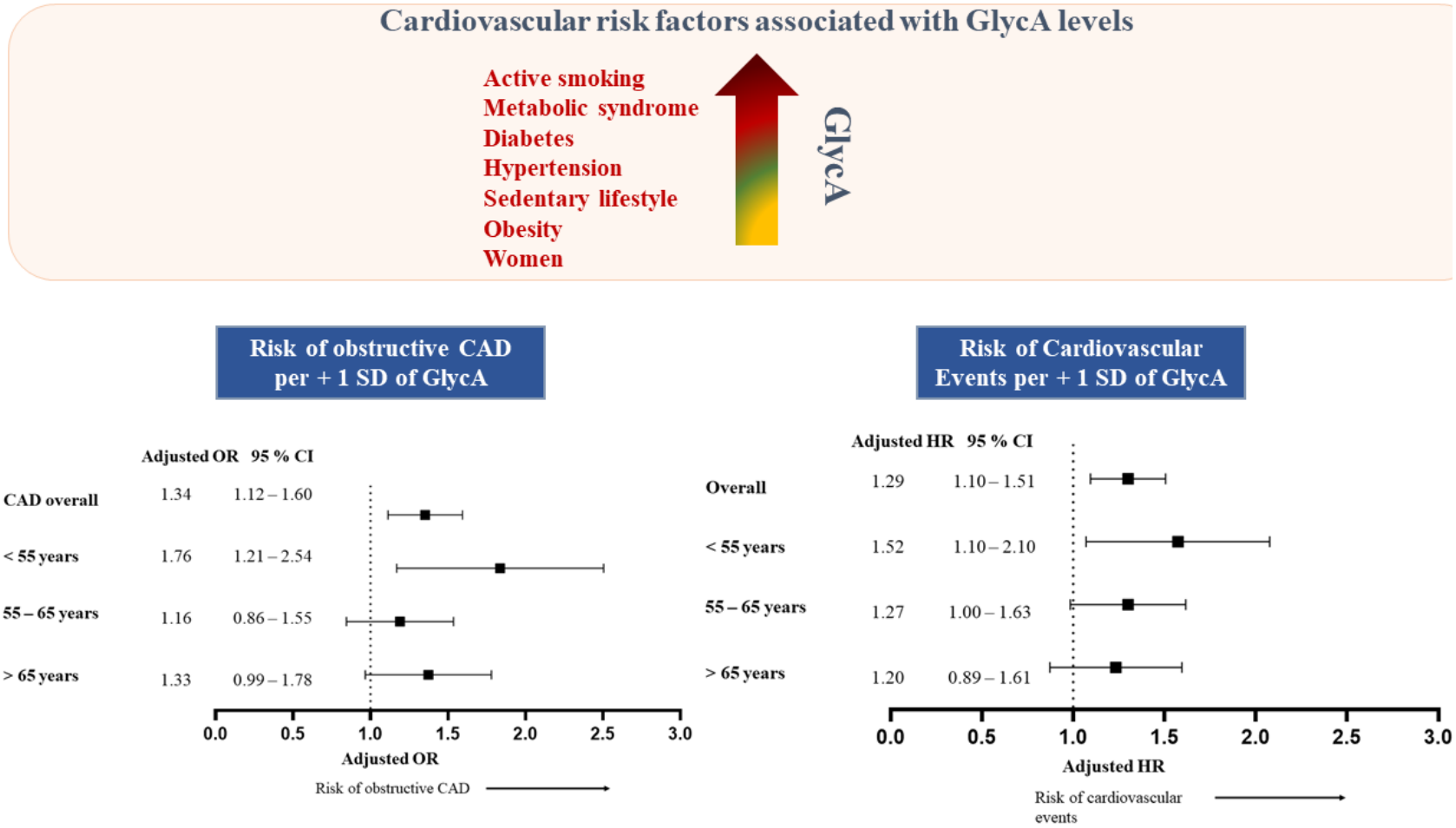
In multivariable analyses stratified by three age-groups, GlycA levels were associated with oCAD only in the premature CAD age group, with the risk of oCAD increased by approximately 76% per standard deviation of GlycA levels (aOR 1.76, 95% CI [1.21-2.54], p=0.003, **Table 3 a**nd **central illustration**). The interaction between GlycA and obstructive CAD remained significant when hs-CRP was included in the model. Formal interaction terms for GlycA and oCAD with age groups was not significant (p = 0.13).

Table 3. Association between oCAD and GlycA (per standard deviation of GlycA)
*adjusted for age, sex, diabetes, hypertension, and current smoking.

**adjusted for age, sex, diabetes, hypertension, and current smoking and hs-cCRP

			Multivariate Model including clinical variables*		**Multivariate Model including clinical variables and hs-CRP****	
Age Group	**Univariate Crude OR**	**P-value**	**Adjusted OR [95% CI]**	**P-value**	**Adjusted OR [95% CI]**	**P-value**
All, n=1798	1.28 [1.08 - 1.51]	<0.01	1.34 [1.12 - 1.60]	0.002	1.30 [1.03 – 1.63]	0.02
<55, n=515	1.66 [1.16 - 2.36]	<0.01	1.76 [1.21 - 2.54]	0.003	1.69 [1.10 – 2.57]	0.01
55-65, n=808	1.09 [0.81 - 1.42]	0.56	1.16 [0.86 - 1.55]	0.33	0.95 [0.64 – 1.41]	0.10
>65, n =475	1.32 [0.99 - 1.75]	0.05	1.33 [0.99 - 1.78]	0.06	1.51 [1.03 – 2.20]	0.03

Central Illustration. Association between GlycA and obstructive CAD and time to cardiovascular events per increase of 1 standard deviation stratified by age groups.



Association between GlycA and CV outcomes

The median follow-up was 2.01 years [IQR: 1.44 – 2.70] in the N=4,019 individuals available in the full biomarker substudy. The composite endpoint of all-cause death, myocardial infarction or re-hospitalization for unstable angina occurred in 125 participants (3.1%). The most frequent event was all-cause death (1.4%), followed by re-hospitalization for unstable angina (1.1%) and myocardial infarction (0.7%). In multivariable analyses, GlycA levels were associated with time-to-cardiovascular events (aHR: 1.29, 95% CI [1.10 - 1.51], p=0.002), mostly driven by all-cause death (aHR: 1.56, 95% CI [1.27 - 1.92], p<0.0001) (**Table 4**). The association between GlycA and cardiovascular events remained consistent after adjustment with hs-CRP. Furthermore, these results remained significant in sensitivity analyses further adjusted for oCAD (**Supplemental Table 1**). A Kaplan-Meier curve of GlycA levels by probability of survival is presented in **Figure 2** (GlycA levels grouped into quartiles for visualization purposes).

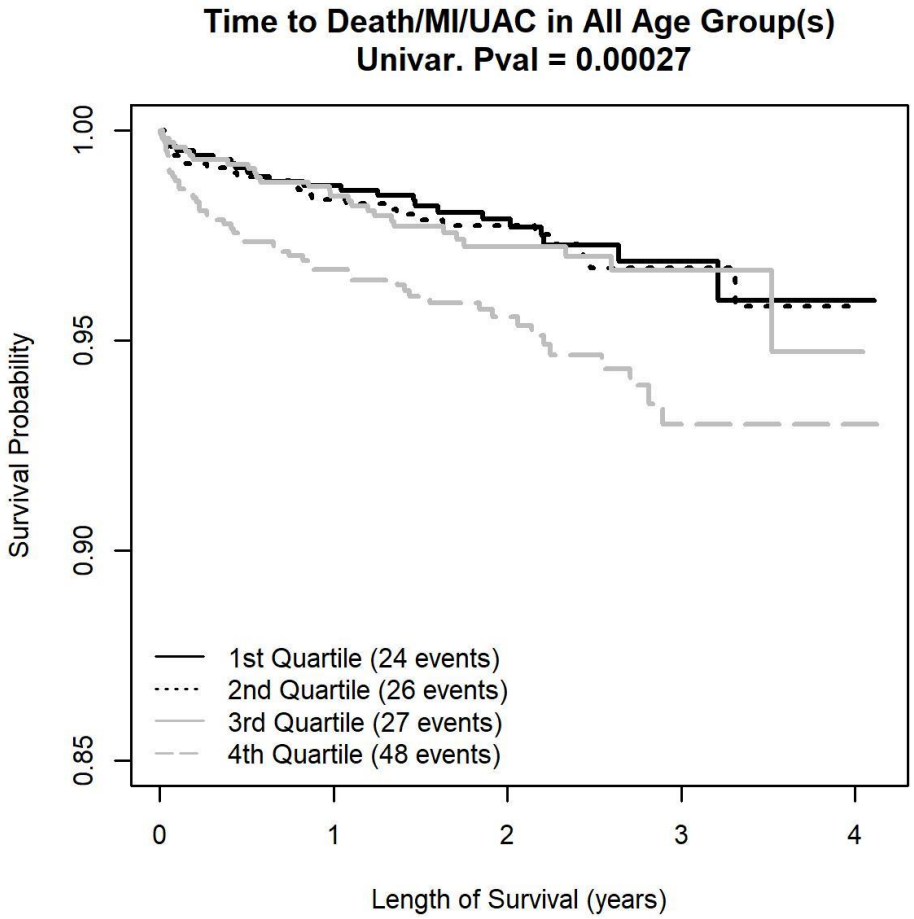
Table 4 Association between cardiovascular events and GlycA (per standard deviations of GlycA)

*adjusted for age, sex, diabetes, hypertension, and current smoking.

** adjusted for age, sex, diabetes, hypertension, and current smoking and hs-CRP

				Multivariate Model including clinical variables*	**Multivariate Model including clinical variables and hs-CRP****
	Event		**Univariate HR [95%CI] P-value**	**Adjusted HR [95%CI] P-value**	**Adjusted HR [95%CI] P-value**
	Yes	**No**			
Composite of all-cause death, MI or unstable angina	125 (3.1%)	3894 (96.9%)	1.34 [1.14 - 1.57] p=0.0003	1.29 [1.10 - 1.51] p=0.0016	1.32 [1.09 - 1.6] P=0.0045
All-cause death	55 (1.4%)	3964 (98.6%)	1.66 [1.35 - 2.05], p<0.0001	1.56 [1.27 - 1.92] p<0.0001	1.58 [1.21 - 2.05] P<0.0001
Myocardial infarction	29 (0.7%)	3990 (99.3%)	0.92 [0.63 - 1.34] p=NS	0.90 [0.60 - 1.33] p=NS.	1.25 [0.78 - 2.01] P=NS
Re-hospitalization for Unstable Angina	43 (1.1%)	3976 (98.9%)	1.22 [0.93 - 1.61] p=NS	1.23 [0.92 - 1.64] p=NS	1.20 [0.85 - 1.69] p=NS

Figure 2. Kaplan-Meier plot of univariate probability of survival without cardiovascular events according to quartiles of GlycA.



With regards to incident events by age, in analyses stratified by enrollment age-group, GlycA was associated with time-to-cardiovascular events only in the youngest <55 yo age group (aHR: 1.52, 95%CI [1.10 – 2.10], p=0.01, (p=0.25, **Table 5 and central illustration**), although the formal interaction term was not significant (p=0.25). Of importance, this association remained significant after adjustment with hs-CRP. In multivariable analyses adjusted for presence of oCAD (CTA group only, n=1,798), individuals in the lowest age group demonstrated the greatest prognostic risk for GlycA levels with events (aHR = 1.56, 95% CI [0.99 - 2.45], p=0.06) (**Supplemental Table 1**).

Table 5. Association between cardiovascular events and GlycA (SD) stratified by age groups.

* adjusted for age, sex, diabetes, hypertension, and current smoking.
** adjusted for age, sex, diabetes, hypertension, and current smoking and hs-CRP

Age Group	Death, myocardial infarction, or unstable angina		Multivariate Model including clinical variables*		Multivariate Model including clinical variables and hs-CRP**	
	Yes	No	Adjusted HR [95% CI]	P-value	Adjusted HR [95% CI]	P-value
All, n=4,018	125 (3.1%)	3893 (96.9%)	1.29 [1.10 - 1.51]	0.0016	1.32 [1.09 - 1.6]	0.0045
Age <55, n=1,118	30 (2.7%)	1088 (97.3%)	1.52 [1.10 - 2.10]	0.01	1.45 [1.01 - 2.09]	0.044
Age 55-65, n=1,768	50 (2.8%)	1718 (97.2%)	1.27 [1.00- 1.63]	0.051	1.34 [0.97 - 1.87]	0.08
Age >65, n=1,132	45 (4.0%)	1087 (96.0%)	1.20 [0.89 - 1.61]	0.23	1.16 [0.82,1.64]	0.41

DISCUSSION

In this biomarker substudy of the PROMISE trial, we find that GlycA, an emerging biomarker of chronic inflammation, is associated (1) with an unfavorable cardiovascular risk factor profile; (2) with obstructive CAD and incident events in patients free of prior cardiovascular disease presenting with stable outpatient chest pain; and (3) with consistent risk across age groups including in individuals with premature CAD.

GlycA levels are composite signals of systemic circulatory cytokines, reflecting the long-term inflammatory status and the overall accumulation of sub-clinical tissue damage by processes like atherosclerosis (155). Because it is a stable marker of the average chronic sub-clinical inflammation, GlycA is considered to be the equivalent of "glycated hemoglobin" for inflammation (155). In this study, we find that individuals with stable outpatient chest pain who had higher GlycA levels were more likely to have hypertension, diabetes, dyslipidemia, metabolic syndrome, or a sedentary lifestyle, reflecting the interaction between health status and sub-clinical inflammation. These observations complement previous findings of the MESA cohort, in which individuals with a favorable cardiovascular risk factors profile - including frequent physical activity, absence of smoking and appropriate body mass index - had lower GlycA levels compared with individuals with unhealthy habits and uncontrolled cardiovascular risk factors (160).

GlycA levels were a more efficient predictor of obstructive CAD than the Diamond and Forrester score. Of importance, this association was independent of CRP levels, reflecting different and more inclusive pathways of inflammation leading to endothelial damage. To our knowledge, this is the first report of an association with a *de novo* diagnosis of obstructive CAD in individuals with stable outpatient chest pain. This association persisted in individuals with premature CAD, bringing more evidence to the important contribution of inflammation in the

development even of premature atherosclerosis, in addition to other traditional risk factors. The implication of inflammation in accelerated atherosclerosis has been well-described, through studies establishing association between biomarkers TNF-α, IL-6, and CRP with atherosclerosis, or in the clinical setting of a chronic inflammatory disease (165, 166). In fact, measurement of inflammatory biomarkers has been a risk enhancer in the latest American cholesterol guidelines (2018) in order to improve cardiovascular risk assessment in borderline or intermediate cardiovascular risk groups and support the prescription of lipid-lowering therapy in primary prevention. The inclusion of novel biomarkers like GlycA is likely to be important for improving the detection of atherosclerosis in non-traditional groups – such as young men and women – especially since ASCVD and Framingham scores have been described as sub-optimal in these populations (139–141).

In addition to the association with obstructive CAD, GlycA was also associated with incident events, driven in particular by all-cause mortality, adding to the body of evidence concerning the role of inflammation as an important part of the residual cardiovascular risk in both primary and secondary prevention (167). Since its first description, GlycA has been described as a significant prognostic biomarker in cardiovascular disease, as well as in cancer and auto-immune disease (156, 158, 168). In a previous study of the CATHGEN database, GlycA levels improved the prediction of major cardiac events on top of traditional cholesterol parameters (159). In a substudy of the JUPITER trial, GlycA improved the prediction of major adverse cardiovascular events, independently of CRP and lipid levels (156).

Sub-clinical inflammation is being increasingly recognized as a major but modifiable contributor to the development of CAD. Targeting systemic inflammation on top of thrombosis and lipids has become an important part of cardiovascular primary and secondary prevention of subsequent cardiovascular events, since the landmark results of the JUPITER trial and subsequent results of the CANTOS trial (151). Stable and specific biomarkers are required to

monitor the effects of interventions promoting appropriate diet, exercise, smoking cessation, and pharmaceutic interventions on sub-clinical inflammation. In a recent study of 169 sedentary young adults with prediabetes, an intervention on life style with moderate to high intensity exercise reduced GlycA concentrations, via modulation of visceral adiposity (169). These observations, along with the present findings suggest that GlycA is a promising and reliable biomarker to detect active atherosclerosis and measure the effects of primary and secondary interventions in healthy individuals at risk and patients with symptomatic atherosclerosis, respectively (20).

LIMITATIONS

We acknowledge several limitations for our study. Firstly, the rate of events was low, limiting power for age-stratified results and interactions. Secondly, our study did not compare GlycA levels to other inflammatory biomarkers. Thirdly, results herein were for individuals without known CAD presenting with stable outpatient chest pain and thus are not generalizable to other patient groups.

CONCLUSIONS

In a population of patients without known CAD presenting with stable outpatient chest pain, higher GlycA levels were associated with oCAD, particularly in individuals with premature CAD, reflecting the important contribution of inflammation in the development of CAD. GlycA was also associated with major cardiac events, with a consistent effect across age groups. These results support the potential role of GlycA as a diagnostic tool to detect active atherosclerosis and a potential therapeutic target especially in young patients.

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Association between GlycA and cardiovascular events when adjusted for oCAD (CTA group).

Age Group	Adjusted HR* [95% CI]	P-value
All	1.10 [0.87 – 1.40]	0.4
<55	1.56 [0.99 – 2.45]	0.055
55-65	1.09 [0.77 – 1.55]	0.6
>65	0.75 [0.44 – 1.26]	0.3

*adjusted for age, sex, diabetes, hypertension, current smoking, and oCAD.

4.Interleukin-1β and Risk of Premature Death in Patients with Myocardial Infarction

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ABSTRACT

BACKGROUND. Inhibition of the interleukin-1β (IL-1β) innate immunity pathway is associated with anti-inflammatory effects and a reduced risk of recurrent cardiovascular events in stable patients with previous myocardial infarction (MI) and elevated high sensitivity C-reactive protein (hs-CRP).

OBJECTIVES. to assess the association between IL-1β level with all-cause mortality in patients with acute ST segment elevation myocardial infarction (MI) undergoing primary percutaneous coronary intervention and the interplay between IL-1β and hs-CRP concentrations on the risk of premature death.

METHODS. IL-1β concentration was measured among 1398 ST segment elevation MI patients enrolled in a prospective cohort. Crude and hazard ratios for all-cause and cardiovascular mortality were analyzed at 90-days and one-year using a multivariate-cox proportional regression analysis. Major cardiovascular events (MACE) were analyzed.

RESULTS. IL-1β concentration measured at admission was associated with all-cause mortality at 90 days (adjusted hazard ratio [adjHR], 1.47 per 1SD increase; 95% CI, 1.16 to 1.87; p<0.002). The relation was nonlinear, and highest tertile of IL-1β was associated with higher mortality rates at 90 days (adjHR: 2.78; 95%CI: 1.61-4.79, p=0.0002) and one-year (adjHR: 1.93; 95%CI: 1.21-3.06, p=0.005), regardless of the hs-CRP concentration. Significant relationships were equally observed when considering cardiovascular mortality and MACE at 90 days (adjHR: 2.42; 95% CI: 1.36-4.28, p=0.002 and 2.29; 95% CI: 1.31-4.01, p=0.004, respectively) and at one year (adjHR: 2.32; 95% CI: 1.36-3.97, p=0.002 and 2.35; 95% CI: 1.39-3.96, p=0.001, respectively).

CONCLUSION. IL-1β measured at admission in acute MI patients is independently associated with the risk of mortality and recurrent MACE.

ABBREVIATIONS

IL-1β: Interleukin-1β

IL-6: Interleukin-6

HR: Hazard Ratio

hs-CRP: High sensitivity C-reactive protein

MACE: Major cardiovascular events

MI: Myocardial Infarction

PCI: Percutaneous Coronary Intervention

INTRODUCTION

High-sensitivity C-reactive protein (hs-CRP) and Interleukin-6 were identified as biomarkers of cardiovascular risk stratification in acute myocardial infarction (MI) patients (171, 172) as they were associated with the size of myocardial infarction and the risk of recurrent events (171). Based on large studies, hs-CRP testing is also recommended in American guidelines to stratify the risk of events among individuals at intermediate risk of atherosclerotic cardiovascular disease (173). The interleukin 1-β (IL-1β) immune innate pathway has generated growing interest as prior studies demonstrated the pivotal role of the proinflammatory cytokine IL-1β in the atherothrombosis process (52, 174). This includes the promotion of monocyte and leukocyte adhesion to endothelial cells, induction of a procoagulant activity, and the growth of vascular smooth-muscle cells (84, 85, 175). Recently, inhibition of IL-1 β with the human monoclonal antibody, canakinumab, led to a reduction of cardiovascular events in stable coronary artery disease patients with both, previous myocardial infarction (MI) and elevated hs-CRP, establishing the proof of concept of the so-called 'inflammatory hypothesis of atherosclerosis (120). In addition, high IL-1β concentrations were recently found to be associated with an increased risk of death in patients with acute heart failure (176, 177). In acute MI patients, there is no information on IL-1β as a risk marker of mortality and no evidence to suggest that targeting IL-1β during the acute phase may impact clinical outcome. In this context, we sought to evaluate whether IL-1 β level, measured during the acute phase of MI, is associated with short- and long-term all-cause mortality and major cardiovascular events in patients hospitalized for mechanical reperfusion of an acute ST-elevation MI.

METHODS

Study population and data collection

A total of 1398 consecutive patients treated for an acute MI were enrolled in the ongoing ePARIS registry, a prospective registry with extensive clinical and biological data collection. Patients were included if they had an acute ST segment elevation MI treated by primary percutaneous coronary intervention (PCI). Biological sampling was obtained at admission in the catheterization laboratory, following sheath insertion. Patients with other final diagnosis were excluded as well as the patients who did not consent to participate. Following revascularization, patients received anti-ischemic, lipid-lowering and antithrombotic drugs according to the current guidelines. Clinical outcomes were obtained from medical reports or by telephone call. In case of loss to follow-up, the survival status was checked in the birth city hall registry.

Study endpoint and objectives

The primary objective was to evaluate the association between IL-1β with all-cause mortality at 90 days. The primary endpoint of the study was all-cause mortality at 90 days. Follow-up was continued until the last patient included reached one year of follow-up. Secondary objectives evaluated the association of IL-1β with i) all-cause mortality at one-year follow-up; ii) cardiovascular mortality up to 1 year; iii) major cardiovascular events defined by the association of cardiovascular death, recurrent MI or stroke, up to 1 year. In an exploratory analysis, we assessed the interplay of IL-1β with hs-CRP on mortality at 90 days.

Blood samples and biochemical measurements

Blood collected was placed into gel-containing vacutainer tubes, centrifuged within 1 hour, and serum was stored at -80°C until used. Serum concentrations of IL-1β were quantified with ELISA Kit (ThermoFisher Scientific) according to the manufacturer's instructions. The limit of detection of human IL-1β is 0.3 pg/ml. For individuals below the level of detection

(n=150) values have been fixed at 0.3 pg/ml. The calculated overall intra-assay and inter-assay coefficient of variation for IL-1β were 3.8% and 5.3%, respectively. Lipids and hs-CRP levels were analyzed on an autoanalyser Konelab 20 (ThermoFisher Diagnostics) and by using commercial kits from Roche Diagnosis for total cholesterol and from ThermoFisher Diagnostics for triglycerides and direct high-density lipoprotein cholesterol (HDL-C) and from Diasys for hs-CRP. The coefficient of variation of hs-CRP for blinded split samples was 4.4%. The level of detection for the CRP was 0.05 mg/L, the intra- and interassay coefficients of variation were 1.7% and 2.5%, respectively. Low density lipoprotein-cholesterol (LDL-C) was calculated using Friedewald formula when triglyceride levels were below 340 mg/dl or by using commercial kit from ThermoFisher Diagnostics for direct LDL-C when triglyceride levels were above 340 mg/dl. Cardiac Troponin I (cTnI; Dade Behring) measurements were performed by immunoassay using an AXSYM analyser (Abbott, Rungis, France).

Study Oversight

The first and last authors (JS and MG) designed the study, gathered and analyzed the data and drafted the manuscript. All the authors vouch for the data and analyses reported. The study conforms to the principles outlined in the declaration of Helsinki. The ePARIS registry was declared to the French ministry of Health and Data Protection Authority (CNIL 1542887v0). Written informed consent was obtained from each patient participating to the registry.

Statistical analyses

Based on an alpha risk of 0.05, a power of 80% and an mean all-cause mortality rate of 8.4% reported previously in a recent analysis of the ePARIS registry (178), we estimated that 1056 patients would be necessary to detect to difference of at least 5% of all-cause mortality between patients with low and high level of IL-1β at 90 days.

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as mean ± standard deviation (SD), whereas continuous variables with skewed distribution (IL-1β, hs-CRP, CPK, cTnI and triglycerides) are given as median and interquartile (Q1-Q3) and were logarithmically transformed prior to analysis. Comparisons between 2 groups of subjects were performed using unpaired Student's t-test or Mann-Whitney test as appropriate. The qualitative variables presented as proportions were compared using the chi-square test. IL-1β and hsCRP levels were analyzed either as continuous variables or as tertiles. Since the 3 pg/ml cut-off point was previously identified as the minimum concentration of IL-1β that can be reliably measured, patients with circulating IL-1β levels< 3 pg/ml served as a reference group (179). Patients with IL-1β levels > 3 pg/ml were divided into tertiles. Patients with circulating hs-CRP levels below 2mg/l served as the reference group (180). Patients with hsCRP levels > 2 mg/l were divided into tertiles. Comparisons across subgroups of circulating IL-1 β levels were analyzed using the Jonckheere-Terpstra trend test. Circulating levels of IL-1β and hsCRP were equally modelled as a binary variable dichotomized below and above the 3rd tertile. A categorical variable was created using all possible combinations of elevated levels of IL-1β and hs-CRP as follows: IL-1β < 3rd tertile and hs-CRP < 3rd tertile (Low-Low); IL-1β > 3rd tertile and hs-CRP < 3rd tertile (High-Low); IL-1β < 3rd tertile and hs-CRP > 3rd tertile (Low-High); IL-1β > 3rd tertile and hs-CRP > 3rd tertile (High-High). The association between variables and all-cause mortality at 90 days and one year were assessed by Cox regression analysis. The variables identified as potential risk markers of all-cause mortality in univariate analysis ($p<0{\cdot}1$) were included in the multivariate cox regression model. Co-variates used in multivariable analysis included: age, gender, creatinine levels, left ventricular ejection fraction <45%, Killip class ≥2, out-hospital cardiac arrest, cardiac-troponin I levels, hsCRP and IL-1β levels, low density lipoprotein-cholesterol levels, high density lipoprotein-cholesterol levels, current smoking, status with

regard to use of statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker and beta blockers. Statistical analyses were performed using the R statistical software computer program. Results were considered to be statistically significant at $p<0{\cdot}05$.

RESULTS

Study population

The flow chart of the study is presented in **figure 1**. A total of 1398 ST segment elevation MI patients treated with primary PCI had an available measurement for IL-1β and were, therefore, included in the analysis. The median time from symptoms onset to blood sampling (sheet insertion) was 300 minutes (IQR: 160- 750). The follow-up of the cohort was complete for all patients at 90 days and at one-year, with a median follow-up of 5.5 years (interquartile range: 1.2 to 8.2 years). During the first 90 days, 117 patients died (8.4%). At one-year, 153 deaths were recorded (10.9%). Baseline characteristics are displayed in **table 1,** according to the survival status.

Figure 1 Flow chart of the study.

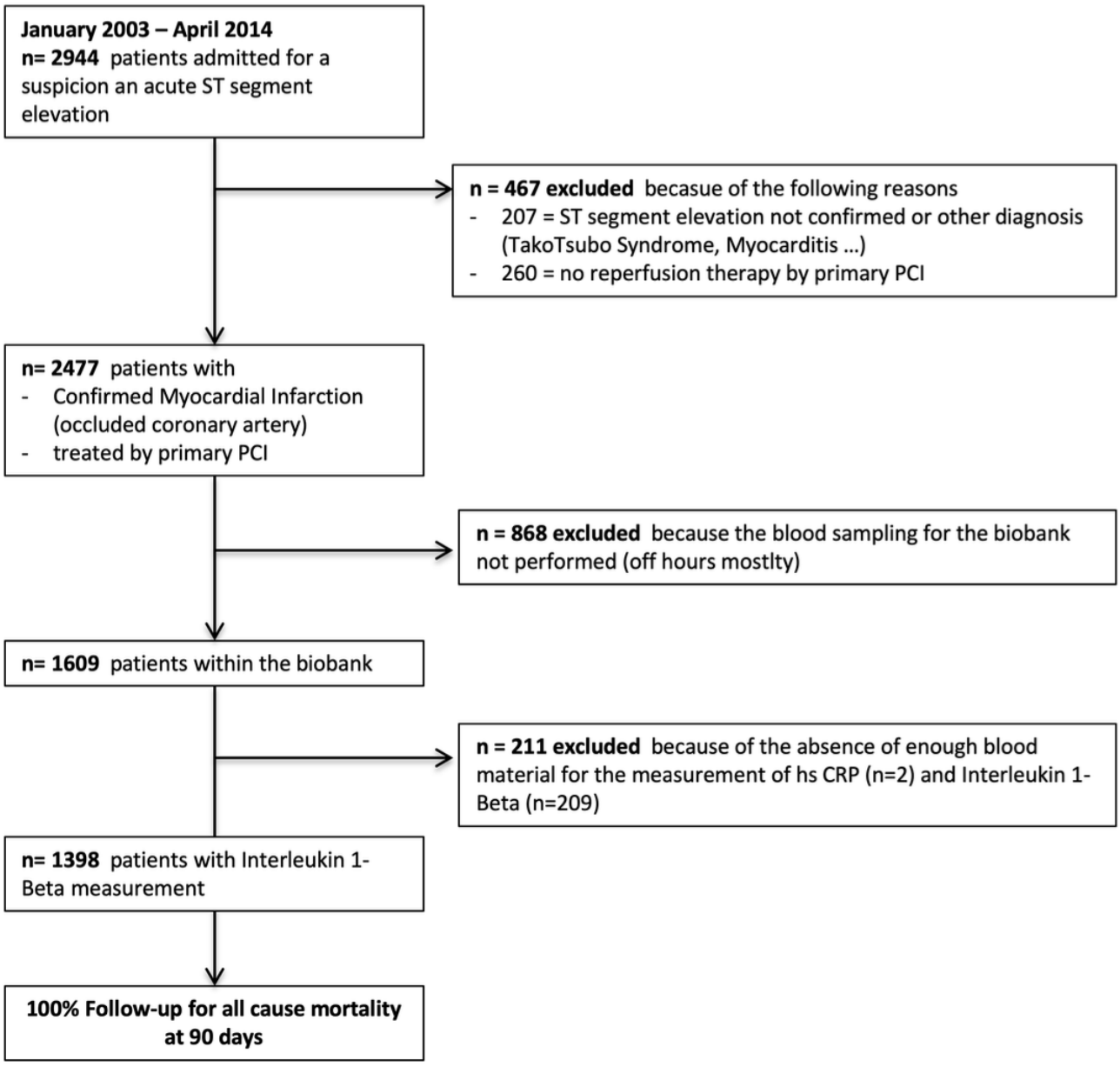


Table 1: Baseline characteristics of the population according to mortality status at 90 days.

	Alive at 90 days (n=1281)	Dead at 90 days (n=117)	P value
Cardiovascular Risk Factor			
Age, year	62.7±13.9	71.6±14.3	<0.0001*
N, (Men/Women)	975/306	71/46	0.0002*
Body Mass Index, (kg/m²)	26.0±4.3	25.5 ±4.5	0.32
Dyslipidemia	43.4%	29.9%	0.0047*
Diabetes	18.3%	18.8%	0.88
Hypertension	47.1%	51.3%	0.38
Smoker	41.9%	19.7%	<0.0001*
Family history of coronary artery disease	21.5%	8.5%	0.0009*
Previous cardiovascular events	19.4%	24.8%	0.16
Cardiac Risk Factor on arrival			
Heart rate (beats per min)	75.6±16.7	86.8±24.1	0.0001*
Systolic Blood Pressure (mmHg)	131.0±25.3	122.0±32.5	0.0010*
Left ventricular ejection fraction	50.6±10.9	36.0±15.3	<0.0001*
Left ventricular ejection fraction <45%	23.2%	66.3%	<0.0001*
Out-of-hospital cardiac arrest	4.0%	47.0%	<0.0001*
Killip class ≥2	12.3%	45.2%	<0.001*
Late Presenter (STB>360 min)	39.1%	37.8%	0.79
Biomarkers			
IL-1β, pg/ml	4.40 (1.59-8.67)	5.19 (2.00-12.21)	0.0482*
IL-1 β >10 pg/ml, %	19.8%	35.0%	0.0001*
hs-CRP, mg/l	5.4 (2.2-23.6)	27.3 (4.7-60.0)	<0.0001*
Creatinine Clearance (ml/min)	85 (60-112)	48 (25-77)	<0.0001*
Creatinine Clearance <60 ml/min	24.7%	63.2%	<0.0001*
CPK, U/L	1195 (400-2543)	1107 (488-3161)	0.46
Cardiac Troponin I, pg/ml	37.1 (10.7-91.7)	48.0 (10.5-139.0)	0.070

Table 1 - suite	**Alive at 90 days (n=1281)**	**Dead at 90 days (n=117)**	**P value**
Triglycerides, (mmol/l)	0.92 (0.66-1.33)	0.93 (0.69-1.40)	0.42
Total Cholesterol, (mmol/l)	4.35±1.12	3.80±1.34	<0.0001*
LDL Cholesterol (mmol/l)	2.93±1.01	2.45±1.22	<0.0001*
HDL cholesterol (mmol/l)	0.90±0.31	0.84±0.31	0.0337*
Discharge Therapy			
Statins	91.5%	43.6%	<0.0001*
Beta-Blockers	84.2%	26.5%	<0.0001*
ACEI/ARB	85.5%	36.8%	<0.0001*

Values are mean±SD or median and interquartile (Q1-Q3). P value indicates significant difference between patients who died or survived at 90 days

Association between IL-1β with all-cause mortality and cardiovascular events

Concentration of IL-1β analyzed as a continuous variable was associated with all-cause mortality at 90 days (adjusted hazard ratio [HR] 1.47 per one SD increase; 95% CI, 1.16 to 1.87; p<0.002). The results of the univariate and multivariate analysis for all-cause mortality at 90 days are presented in **table 2.** After adjustment for all factors associated with mortality including cardiovascular risk factors and established prognostic factors including LDL cholesterol, troponin and hs-CRP level, the Cox proportional hazards regression analysis identified that elevated IL-1β levels were significantly associated with a higher risk of death (**Figure 2**). According to tertiles of IL-1β concentrations, the mortality rate at 90 days was higher among patients at the highest tertile compared with the reference group (adjHR: 2.77; 95% CI: 1.49-5.16, p=0.0013, **figure 3A and Supplemental Table S1**).

Table 2: Association between variables and of all-cause mortality at 90 days in univariate and multivariate Cox regression analyses

	Univariate Analysis		Multivariate Analysis	
Variables	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Interleukin-1 β, pg/ml	1.20 (1.06 – 1.35)	0.0039	1.47 (1.16 – 1.87)	0.0015*
hs-C-Reactive Protein, mg/l	1.85 (1.48 – 2.31)	<0.0001	1.50 (1.06 – 2.11)	0.0205*
Male Gender	0.50 (0.34 – 0.72)	0.0002	0.92 (0.50 – 1.67)	0.78
Age	1.88 (1.55 – 2.28)	<0.0001	1.75 (1.22 – 2.50)	0.0021*
Creatinine	1.56 (1.40 – 1.75)	<0.0001	1.38 (1.12 – 1.71)	0.0023*
CPK, U/L	1.05 (0.85 – 1.30)	0.67	-	-
LVEF <45%	6.03 (3.80 – 9.59)	<0.0001	2.20 (1.24 – 3.90)	0.0073*
Killip class ≥2	5.28 (3.59 – 7.77)	<0.0001	1.15 (0.66 – 2.02)	0.61
STB time >360 min	0.95 (0.65 – 1.39)	0.79	-	-
Out-Hospital cardiac arrest	14.6 (10.2 – 21.1)	<0.0001	12.1 (6.24 – 23.6)	<0.0001*
History of MACE	1.40 (0.92 – 2.14)	0.11	-	-
Cardiac Troponin I, pg/ml	1.27 (1.00 – 1.60)	0.0461	1.34 (1.00 – 1.80)	0.0468*
Triglycerides	1.05 (0.88 – 1.26)	0.57	-	-
LDL-Cholesterol	0.60 (0.49 – 0.73)	<0.0001	1.09 (0.85 – 1.40)	0.48
HDL-Cholesterol	0.81 (0.66 – 0.98)	0.0357	1.00 (0.75 – 1.34)	0.97
Diabetes	1.02 (0.65 – 1.63)	0.92	-	-
Hypertension	1.18 (0.82 – 1.69)	0.37	-	-
Obesity	1.10 (0.66 – 1.84)	0.71	-	-
Smoking	0.35 (0.22 – 0.55)	<0.0001	1.14 (0.56 – 2.31)	0.72
Statins	0.09 (0.06 – 0.13)	<0.0001	0.44 (0.22 – 0.91)	0.0272*
Beta-blockers	0.08 (0.05 – 0.12)	<0.0001	0.20 (0.10 – 0.40)	<0.0001*
ACEI/ARB	0.11 (0.08 – 0.16)	<0.0001	1.11 (0.51 – 2.42)	0.78

Figure 2: Adjusted Cox proportional Hazards regression analysis of all-cause mortality at 90 days according to IL-1β levels. The Blue line indicated the adjusted Hazard Ratio (HR) and the dotted line the 95% confidence interval (CI).

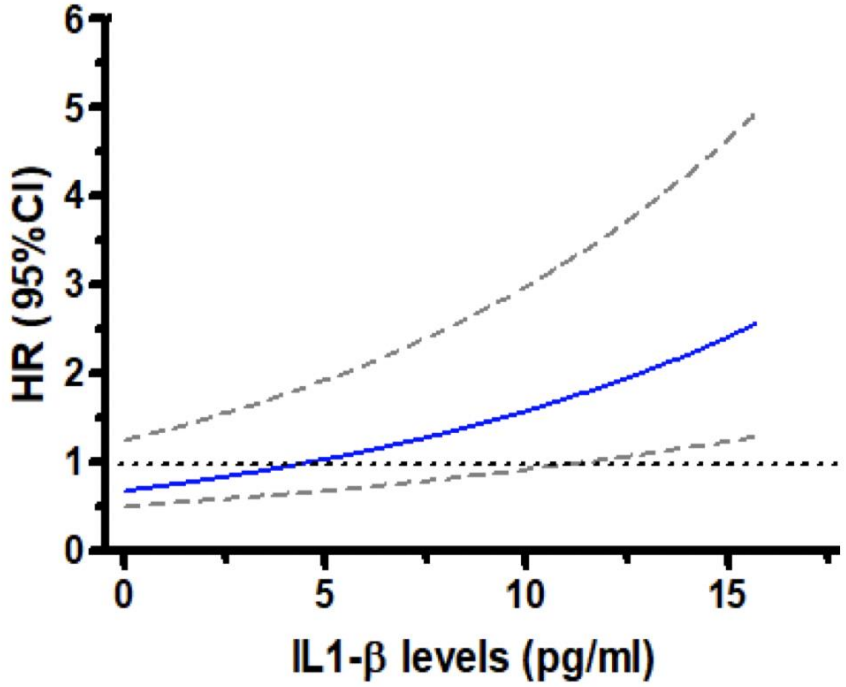
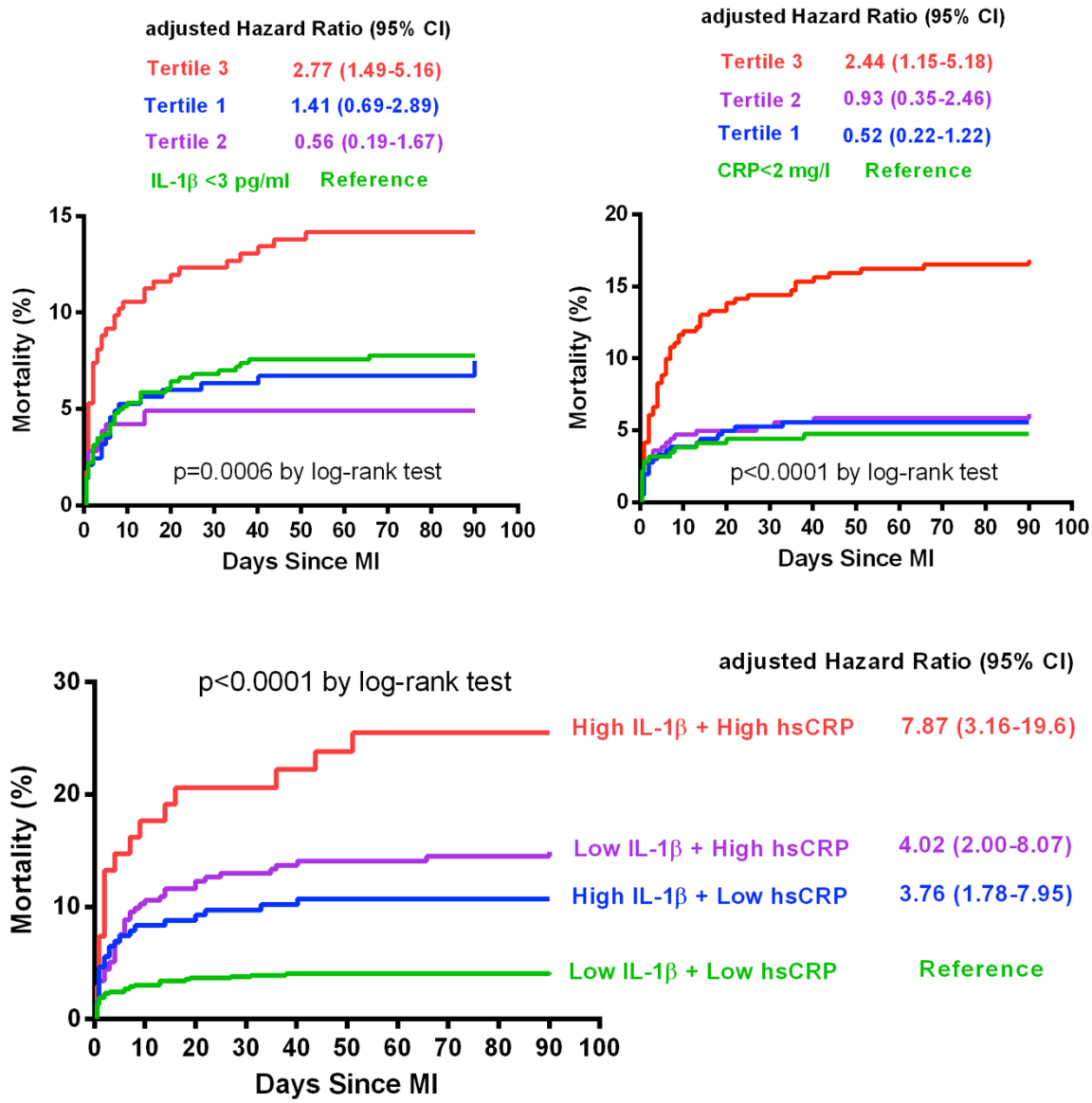
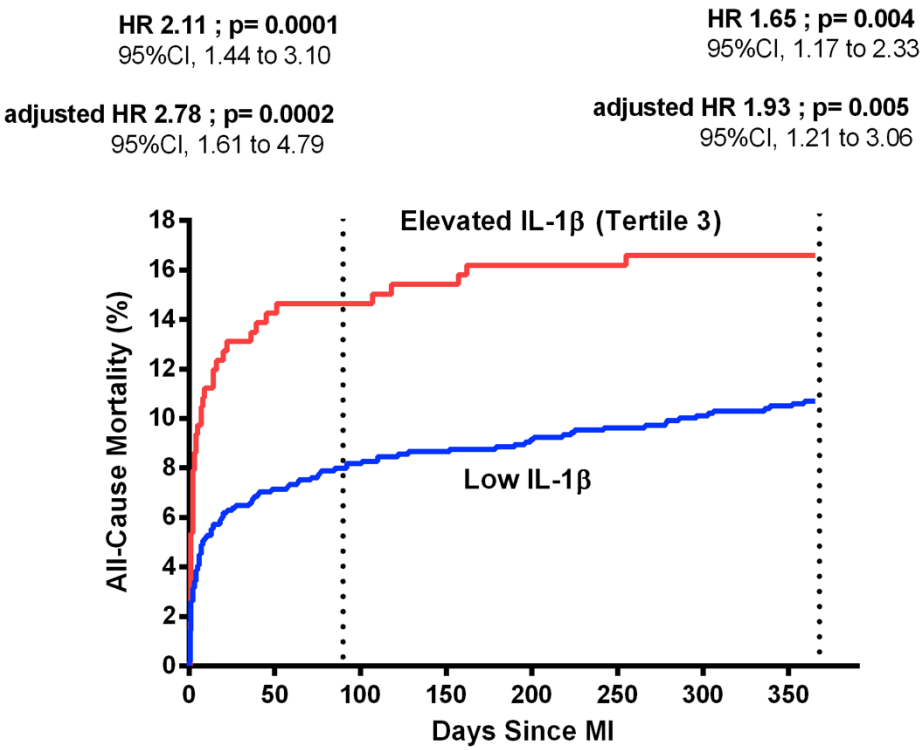


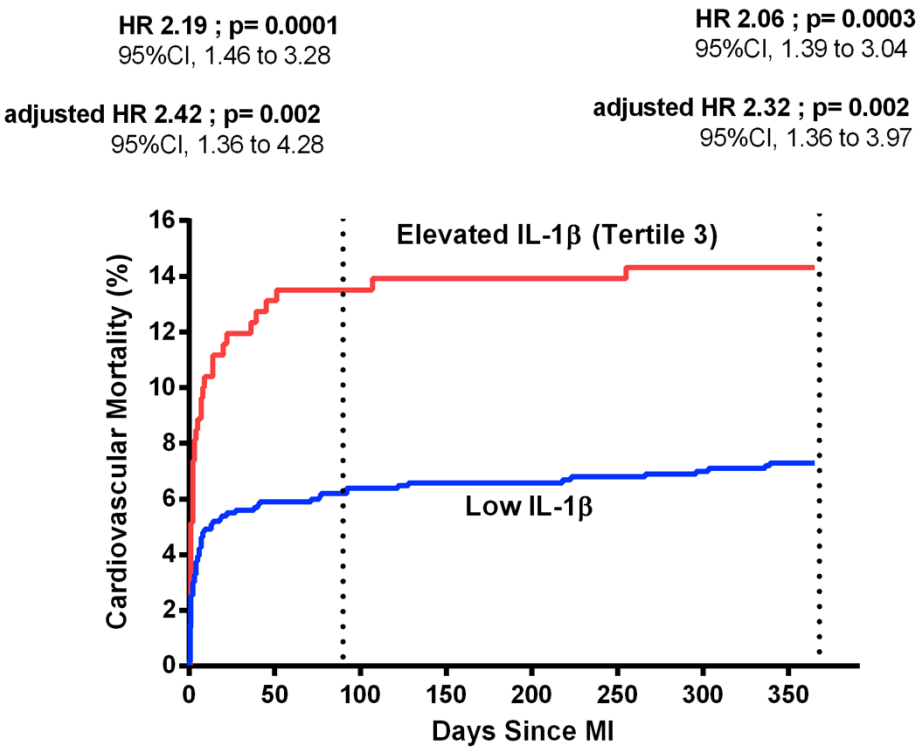
Figure 3.- Central Illustration- Kaplan-Meier cumulative survival curve for all-cause mortality at 90 days according to IL-1 β tertiles (Panel A), hs-CRP tertiles (Panel B) and according to combination categories of risk (high and/or low) based on elevated IL-1 β (>3rd tertile) and elevated hs-CRP (> 3rd tertile) levels (Panel C). Adjusted (Cox) Hazard ratio (HR) are provided with 95% confidence intervals (CI).



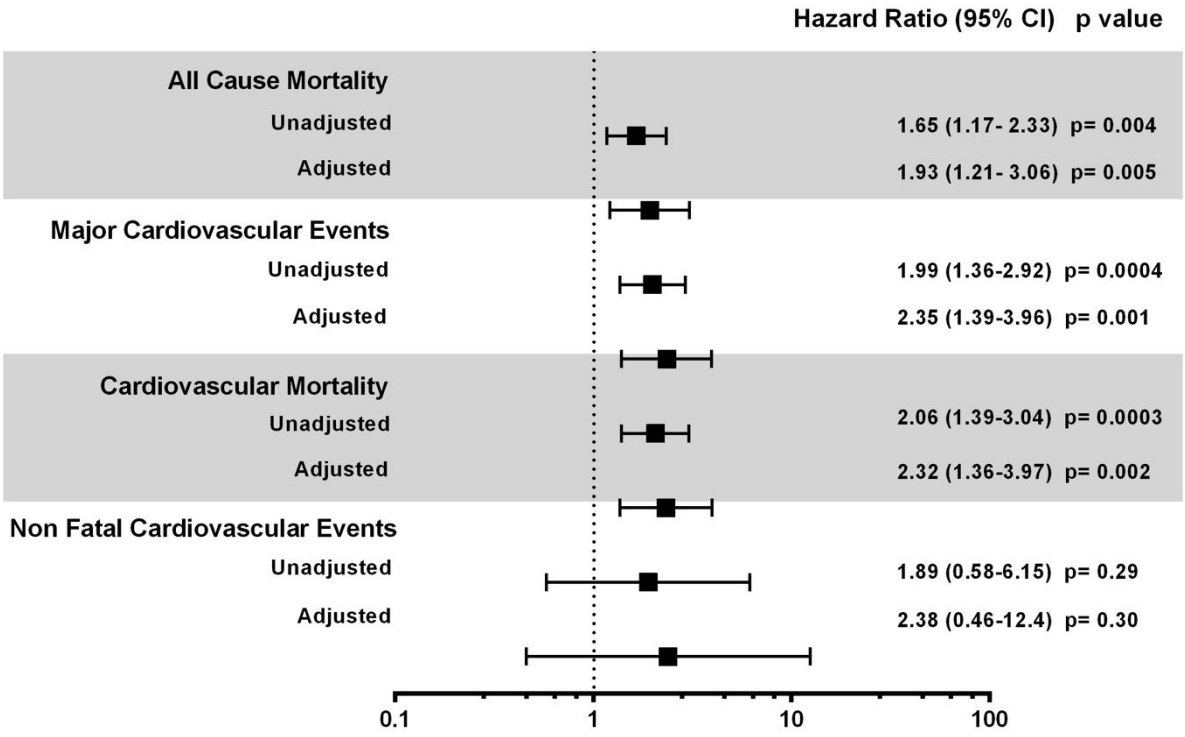
Kaplan-Meier survival curves for 90 days and one-year mortality (all cause and cardiovascular) showed that patients with elevated IL-1β levels (> Tertile 3) at admission had a marked increased risk of mortality at 90 days and one year compared to those with lower IL-1β levels (< Tertile 3) (**figure 4**). The analysis of major cardiovascular events showed that the majority of all-cause deaths were cardiovascular deaths (80%) and that cardiovascular mortality and MACE at 90 days were associated with IL-1β concentration (adjHR: 2.42; 95% CI: 1.36-4.28, p=0.002 and 2.29; 95% CI: 1.31-4.01, p=0.004, respectively for patients with IL-1β concentration higher than the third tertile). Results were consistent and even stronger at one-year follow-up **(Figure 5)**. Results for non-fatal cardiovascular events showed a similar trend (NS, figure 5).

<u>Figure 4 :</u> Kaplan-Meier cumulative survival curve for All-cause mortality (A) and Cardiovascular Mortality (B) at 90 days and one year according to elevated concentration of IL-1 β (> 3rd tertile 3). Crude (log rank) and adjusted (Cox) Hazard Ratio (HR) are provided with 95% confidence intervals (CI).





<u>Figure 5:</u> Hazard Ratios at 1 year according to elevated concentration of IL-1 β (> 3rd tertile 3). Patients with circulating IL-1β levels < 3rd tertile served as a reference group. Crude (log rank) and adjusted (Cox) Hazard Ratio (HR) are provided with 95% confidence intervals (CI).



Interplay between hs-CRP levels, IL-1β and 90 days mortality

Median hs-CRP level at admission was 5.8 mg/l (2.3-26.8). A marked increased risk of all-cause mortality at 90 days was observed in patients with elevated hs-CRP levels (highest tertile) as compared to the reference group (adjHR: 2.44; 95% CI: 1.15-5.18, p<0.02, **figure 3B).**

In the study population, 58.7% (n=821) of patients displayed low levels (<3rd tertile) of both hs-CRP and IL-1β. In contrast, 4.9% (n= 68) of the population had elevated levels (>3rd tertile) of both IL-1β and hs-CRP. Kaplan-Meier survival curves for 90 days according to combination categories of risk based on both IL-1β and hs-CRP levels (below or above the 3rd tertile) show the association between all-cause mortality and inflammatory profile **(figure 3C).** Patients with elevated IL-1β levels (>3rd tertile), with or without concomitant elevated hs-CRP, had a higher risk of mortality at 90 days than those with low concentrations (<3rd tertile) of both IL-1β and hs-CRP.

DISCUSSION

In this prospective cohort study of homogeneous and well characterized acute MI patients, we demonstrate that IL-1 β concentration at admission is independently associated with all-cause mortality. We demonstrate that this relationship is not linear and is driven by the markedly increased risk of premature death during the first 90 days among patients with the highest level of IL1- β. Finally, both cardiovascular death and MACE were associated with high level of IL-1β and our results suggest that IL-1 β concentration can risk stratify acute MI patients in a synergic fashion with hs-CRP.

Although our findings do not provide mechanistic explanations for the link between IL-1β and mortality, the data on the association of inflammation and myocardial damage are accumulating. Indeed, at the early phase of MI, IL-1β plays an important role during myocardial ischemia-reperfusion injury (181), that may impact short term outcomes of patients undergoing revascularization by primary PCI. Inhibition of IL-1β resulted in attenuated inflammatory injury and, in-vitro, protected cells from IL-1β -induced apoptosis, suggesting an effect on myocardial preservation (182). Prior study has also demonstrated that targeting IL-1β following coronary artery ligation decreased the leukocyte production, inflammation and finally reduced the risk of post-MI heart failure in ApoE (-/-) mice with atherosclerosis (183). Additionally, IL-1 β was associated with an increased risk of death in a recent cohort of patients with acutely decompensated heart failure (176).

Three drugs, canakinumab, anakinra and rilonacept, are now approved by the United States Food and Drug Administration to inhibit the IL-1 pathway making IL-1β a prognostic and therapeutic target in coronary patients (184). Indeed, canakinumab, a monoclonal antibody neutralizing IL-1β was shown to reduce hs-CRP and the risk of recurrent ischemic events in stable patients with prior MI (233). The discrepancy between levels of IL-1β and CRP observed in our study may be explained by different kinetics in the release of these biomarkers that is

unknown in acute myocardial infarction patients and would have required serial measurement of biomarkers of the inflammatory response to fully explore this hypothesis. However, from a physiologic and clinical perspective, IL-1β, and CRP should be interpreted as parts of the same the central NLRP3 to IL-1 to IL-6 to CRP signaling pathway of innate immunity, that have at the end, the same pro-atherothrombotic effect. Further, in the CANTOS trial, the impact of IL-1β inhibition on the reduction of clinical events was directly related to the magnitude of both IL-6 and CRP reduction achieved (185, 186). Anakinra, an IL-1 receptor inhibitor, can also effectively reduce inflammation and possibly the incidence of heart failure in patients with myocardial infarction, with or without CRP elevation (187, 188). This effect would be consistent with the results of the prespecified analysis of the CANTOS trial that demonstrated a signal toward a dose-dependent reduction in heart failure outcomes (86). More importantly, these findings should be put in perspective with the recent results of the randomized, placebo controlled, COLCOT trial, that demonstrated a reduction of ischemic cardiovascular events in acute MI patients treated with colchicine, a drug that target nonspecific inflammation through NLRP3 inflammasome and IL-1β axis (134). These results are promising for the potential use of these anti-inflammatory drugs in MI patients, although none of these interventions were biomarker-guided using CRP or the level of IL-1β.

The present study has limitations and biases inherent to registries. First, despite adjustment for variables known to be associated with all-cause mortality, we may have unmeasured cofounding variables in this analysis. Second, clinical outcomes were not adjudicated, but obtain from medical records, telephone follow-up or national vital statistics system when necessary. Third, IL-1β measurement varies widely across assay platforms and our findings need to be validated in an external cohort. Fourth, IL-6 was not measured and may be superior to CRP or IL-1β to predict the risk of outcomes among patients with ST segment elevation MI (189). However, all these biomarkers provide information on the central NLRP3 to

IL-1 to IL-6 to CRP signaling pathway of innate immunity and this analysis highlight the key role of IL-1 in the inflammatory process involved during acute myocardial infarction.

CONCLUSIONS

Our study demonstrates that high IL-1β at admission is associated with all-cause mortality, cardiovascular mortality and, MACE in an unselected acute MI population undergoing primary PCI. Elevated IL-1β levels identifies patients at higher risk of mortality at 90 days. This study reinforces the need to further evaluate the benefit of IL-1β inhibitors in patients with acute MI possibly with a selective IL-1β guided approach for treatment

5.Reduced Proximal Aortic Distensibility is related to recurrent ischemic events in Young Adults with Premature Coronary Artery Disease

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ABSTRACT

BACKGROUND. While overall mortality from coronary artery disease (CAD) is decreasing, this trend does not extend to younger patients. Reduced distensibility of proximal aorta is related to mortality and incident ischemic events in the general population but has not been studied in premature CAD.

OBJECTIVES. To evaluate the association between aorta distensibility and major adverse cardiovascular events (MACE) in patients with premature CAD.

METHODS. Ascending (AAD) and descending (DAD) aorta distensibility were measured in magnetic resonance imaging (MRI) with comcomitant central blood pressures in the AFIJI prospective registry (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) including patients with CAD diagnosed before the age of 45 years. Association between ascending and descending aorta distensibility and the occurrence of MACE was evaluated. MACE were defined as the composite of cardiovascular death, myocardial infarction (MI) – first MI or recurrent MI-, refractory angina requiring revascularization, and ischemic stroke.

RESULTS. A total of 150 patients who underwent cardiac MRI between April 2014 and December 2019 were included. Median follow-up was 3.0 years. MACE occurred in 24 (16%) patients with a median delay of 311 days. In univariate analysis, reduced AAD was associated with the occurrence of MACE (median 5.27 [2.78 - 6.82] $mmHg^{-1}.10^{-3}$ for patients who presented at least one MACE, versus 6.19 [4.67 - 7.94] $mmHg^{-1}.10^{-3}$ in patients without MACE (p=0.02), but there was no significant association between descending aorta distensibility and MACE. After adjustment for age at MRI, active smoking at baseline and multivessel CAD, reduced AAD remained significantly associated with MACE (adjusted OR of 1.32 [1.02, 1.69] per decrease of 1 $mmHg^{-1}.10^{-3}$ of AAD).

CONCLUSIONS. Altered ascending aorta distensibility measured by MRI was associated to the occurrence of MACE in patients with premature CAD before the age of 50 years independent of age, blood pressure, active smoking and multivessel CAD. Ascending aorta distensibility may be a novel marker of personalized risk in premature CAD.

ABBREVIATIONS

AAD	Ascending aorta distensibility
ADD	Descending aorta distensibility
ACE/ARB	Angiotensin-Converting Enzyme / Angiotensin II Receptor Blockers
AFIJI	Appraisal of risk Factors in young Ischemic patients Justifying aggressive
CAD	Coronary Artery Disease
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MESA	Multi-Ethnic Study of Atherosclerosis
MRI	Magnetic Resonance Imaging

INTRODUCTION

Despite important advances in primary and secondary cardiovascular prevention, that has reduced the burden of cardiovascular disease in Europe and Northern America over the past few decades, the rate of young patients with myocardial infarction (MI) is increasing (64). Young patients with premature coronary artery disease (CAD) is currently the only category of patients with no reduction in mortality after MI (190, 191), and carry the burden of an aggressive and evolutive chronic disease with a high rate of ischemic recurrence and rapid evolution towards a multivessel disease (51, 121).

Furthermore, challenges remain regarding the individual risk stratification of these younger patients for which current strategies based on clinical scores and biological markers seem insufficient (139, 140, 192), highlighting the need for novel tools. Among recent markers for cardiovascular risk stratification, the measure of proximal aorta distensibility by magnetic resonance imaging (MRI) is one of the earliest quantitative phenotypes to be altered in a lifetime, in asymptomatic individuals and related to left ventricular remodeling, even in the absence of significantly increased blood pressure levels (193). Imaging studies have demonstrated that proximal aortic distensibility is associated with physiological aging and is an integrative marker of arterial alterations (194–197), influenced by risk factors and markers such as sedentary lifestyle, obesity, diet, hypertension, smoking, diabetes and dyslipidemia.

Longitudinal prospective cohort studies have demonstrated that proximal aortic distensibility is associated with all-cause mortality and cardiovascular events in adults over 45 years free of overt cardiovascular disease (87). In the MESA study, proximal aortic distensibility was related to incident ischemic cardiovascular events only in low to intermediate risk individuals without known cardiovascular disease which included most of the younger age group at baseline from 45 to 55 years. However, proximal aortic distensibility and its association with cardiovascular outcomes have not been described in a younger population with premature CAD.

The present study aims to evaluate the association between proximal aorta distensibility and cardiovascular outcomes inpatients with premature CAD.

METHODS

Study design and eligibility

The present study included consecutive patients of the AFIJI cohort (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) with a dedicated cardiovascular MRI aiming to measure proximal aortic distensibility. The AFIJI prospective cohort of patients with premature CAD has been previously described (121). In brief, patients under 45 years who survived an inaugural first CAD event were enrolled in the AFIJI multicenter cohort from the 1st of April 1996. Premature CAD was defined as the occurrence of an acute myocardial infarction (MI) or a symptomatic myocardial ischemia with one or more angiographic coronary stenosis ≥70% before the age of 45 years. Suspicion of MIs without obstructive CAD at angiography that were not confirmed by ischemia or necrosis at MRI were excluded from the registry, as well as myocarditis, hyperadrenergic cardiomyopathies and coronary spasms. In this study, only patients of the AFIJI registry who had cardiac MRI were included. All patients included in the AFIJI registry signed an informed consent.

Before January 1st 2016, cardiac MRI was performed during follow-up at the request of the referring cardiologist and additional imaging of the thoracic aorta was performed. After January 1st 2016, cardiac MRI was performed systematically between 1 and 6 months after the inaugural CAD event that justified the inclusion in the AFIJI cohort. Patients who had cardiovascular MRI beyond 5 years after the inaugural CAD event were excluded, so as to minimize the potential effect of aging on the measure of ascending aorta distensibility (198).

Aortic and cardiac MRI

Cardiac MRI with pharmacological stress test was performed using 1.5-T whole-body MRI scanners SOMATOM AERA (Siemens Healthineers®, Germany) in the Cardiovascular and Thoracic Imaging Department, Cardiology Institute, La Pitié Salpêtrière Hospital, Paris, France. Central aortic pressure was measured simultaneously to aortic strain imaging with a brachial blood pressure cuff, using a calibrated system using a validated transfer function (Sphygmocor®, AtCor, Australia).

Cross-sectional cine SSFP images of the thoracic aorta were acquired perpendicular to the vessel centerline on the ascending aorta at the level of the center of the right pulmonary artery with the following typical parameters: 60 phases, average temporal resolution 15 ms depending on the heart rate, slice thickness: 8mm, acquisition matrix: 256x166. Contours of the ascending and descending aorta were automatically detected and traced using the validated software ArtFun+® (Imageens, France) based on ArtFun, (INSERM, France) (199).

All measurements were performed independently by the cardiovascular imaging core lab blinded to clinical data. Ascending (AAD) and descending (DAD) aortic distensibility were calculated as: (As−Ad) / Ad×PPc in 10^3.$mmHg^{-1}$, where As et Ad are respectively maximal systolic and diastolic aortic cross sectional areas in mm^2 and PPc is central pulse pressure in mmHg.

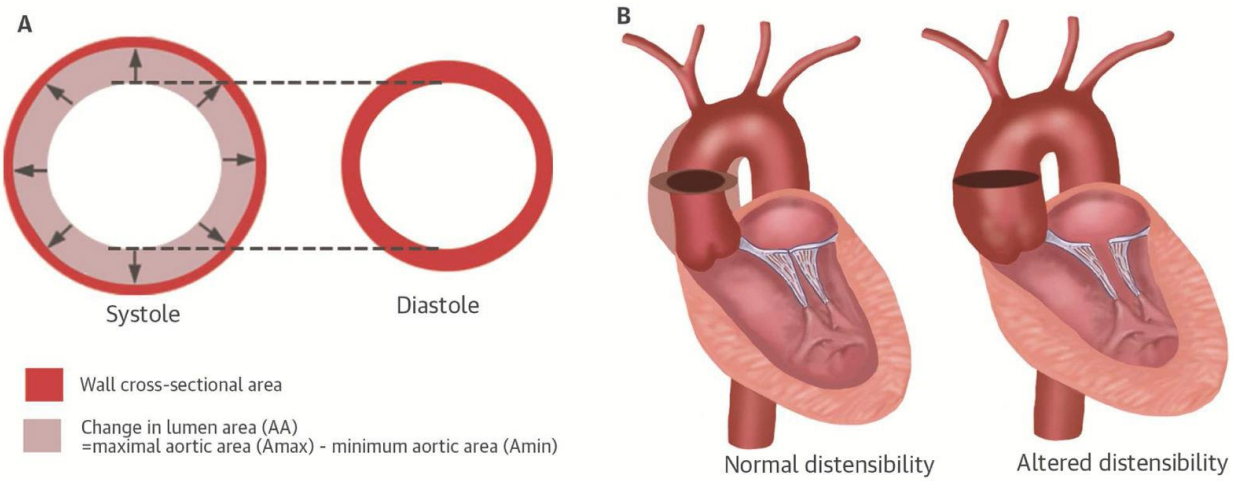


Illustration from Redheuil et al., Proximal aortic distensibility is an independent predictor of all-cause mortality and incident CV events: the MESA study. J Am Coll Cardiol 2014;64(24):2619–29. Doi: 10.1016/j.jacc.2014.09.060.

Data collection and follow-up

This prospective study was approved by the local ethics committee, sponsored by Assistance Publique-Hôpitaux de Paris, supported by the ACTION Study Group. All patients provided a written informed consent before enrollment. Participants were followed by general cardiologists with regular visits to participating tertiary centers (at least every 2 years). All information was collected and updated for each patient, whether or not they presented a new cardiovascular event. Last follow-up was collected in July 2020. At baseline, traditional cardiovascular risk factors and treatments were recorded, but also the presence of chronic inflammatory or immunosuppressive disease—such as Human Immunodeficiency Virus infection, viral hepatitis, or any other chronic inflammatory disease, including cancer.

Baseline and repeated coronary angiograms were reviewed by independent investigators at the ACTION study group angiography core laboratory.

Study objectives

The primary objective was to assess the association between the occurrence of ischemic events in patients with established premature CAD and proximal aortic distensibility of the ascending and descending thoracic aorta measured by MRI using simultaneous central blood pressures.

The secondary objective was to describe proximal aortic distensibility (of the ascending and proximal descending aorta) in this specific population.

Endpoint definitions

Incident ischemic events were defined as the occurrence of Major Adverse Cardiac Events (MACE), a composite of cardiovascular death, myocardial infarction (MI) – first occurrence after diagnosis of stable angina or recurrent MI-, refractory angina requiring revascularization, and ischemic stroke. Cardiovascular death was defined as death resulting from MI, or stroke or cardiac failure or a cardiac procedure. Sudden death without clear non-cardiovascular cause was considered as a cardiovascular death. Clinical endpoints were adjudicated by two clinicians. MI was defined according as type 1 according to the Third Universal Definition of 2012 (200). Ischemic stroke was defined as an acute focal or global neurological deficit resulting from a cerebral infarction proven on cerebral imaging.

Statistical analysis

Continuous variables are presented as means and standard deviations (±SD) or medians and interquartile ranges. Variable distributions were checked for normality. Normally distributed variables were compared using Student's t-test and non-normally distributed variables using the Mann-Whitney U test. Comparisons of more than two continuous variables were performed using the ANOVA test if normally distributed, otherwise comparisons were performed using a Kruskal Wallis rank test. Categorical variables are presented as counts and percentages and

compared using the chi-square test or Fisher's exact test in case of low number of events. First, we compared the present sample of the AFIJI cohort who performed cardiac MRI with the total AFIJI cohort. Participants were classified and compared according to quartiles of ascending and descending aorta distensibility. The purposes of dividing the cohort in quartile ranges were was to describe the population's characteristics and to identify factors associated to the variation of ascending aorta distensibility (AAD) and descending aorta distensibility (DAD), which are continuous variables. Cumulative incidence rates were calculated and expressed as the number of new cardiovascular events divided by the number of patient-years of follow-up (number of events per 100 patient-years). Participants were then classified and compared according to the occurrence during follow-up of a MACE, as defined above. Logistic regression was used to assess independent relationship after adjusting for covariates. Two separate logistic regression models were described for ascending and descending aorta distensibility, both adjusting for variables already described as being associated with MACE in the AFIJI cohort, *i.e.* active smoking and multivessel disease, as well as calendar age, as aortic distensibility is closely related to age (201). Of note, diabetes mellitus, chronic inflammatory disease and ethnicity (from subsaharian Africa) were also, albeit to a lesser degree, associated with the occurrence of ischemic recurrence in the AFIJI cohort but these characteristics were too scarce to be reliably integrated to the multivariate model. Statistical analysis was performed using R (R Foundation, Vienna, Austria) with RStudio Server version 3.6.1 (RStudio Inc., Boston, Massachusetts). The statistical significance threshold was 0.05 and confidence intervals were expressed at 95%.

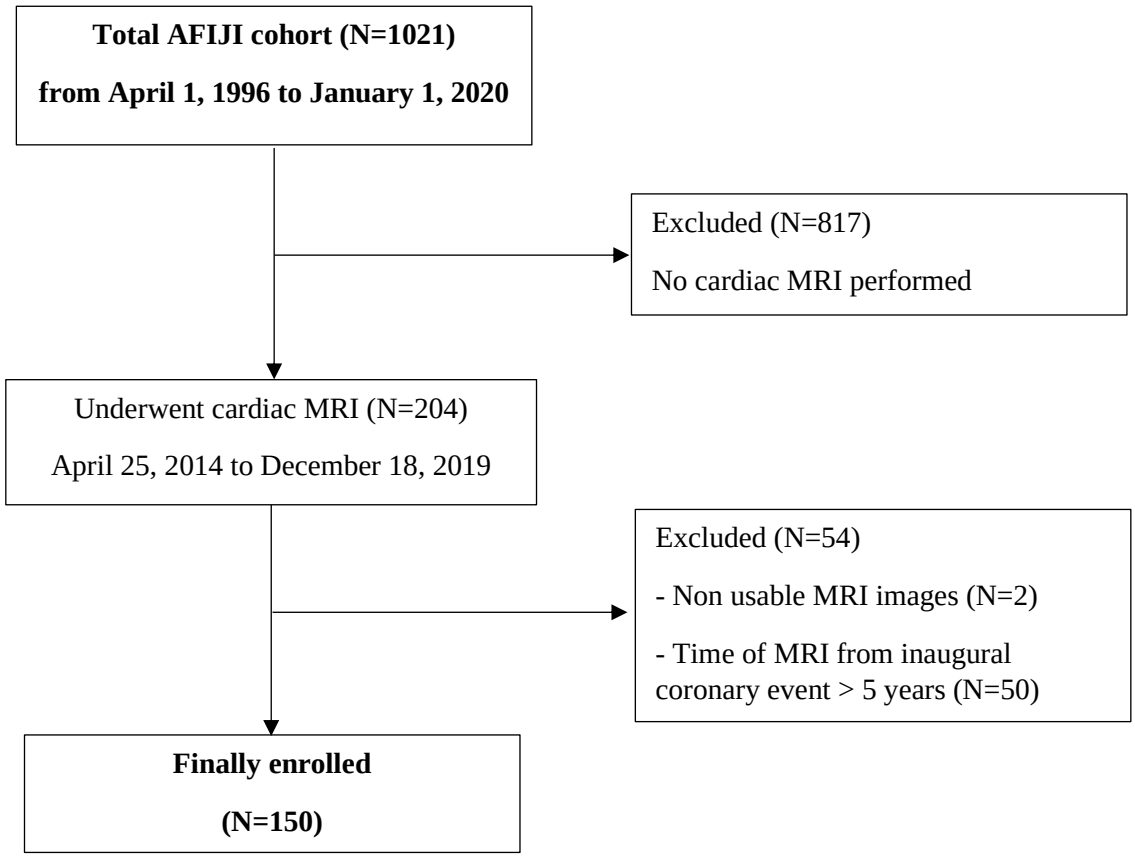
RESULTS

Baseline clinical characteristics

Among the AFIJI cohort on the 1st of January 2020, a total of 204 patients underwent a cardiovascular MRI before the age of 50 years, with a measurement of proximal aorta

distensibility, between April 2014 and December 2019. Among the 204 eligible patients, 150 were finally included in this study. Two patients were excluded because of non-exploitable MRI images, and the other 52 patients were excluded because MRI was performed more than 5 years after the first coronary event **(see flowchart, figure 1).**

Figure 1. Study flow chart



Median follow-up from inclusion was 3.0 years (IQ: 1.5 – 4.3). Median age at the initial diagnosis of CAD was 42.1 years (IQ: 36.4 – 44.5). Patients were mostly males (88%), half of them had a family history of CAD (47.4%) and were active smokers (51.3%) at CAD diagnosis. Hypertension concerned 22% of patients and diabetes mellitus 12.0% of patients (Table 1). Only 7 patients (5%) had a history of chronic inflammatory disease or were under immunosuppressive medication. Myocardial infarction was the main first manifestation of CAD justifying inclusion in the cohort (89.3%). One out of three patients (32%) had a multivessel disease (≥ 2 vessels). Left ventricular ejection fraction (LVEF) was mostly preserved, as only 2 patients had an LVEF<40%. The vast majority of patients was treated with beta-blockers (77%) and angiotensin-converting enzyme angiotensin II receptor blockers (ACE/ARB) (67%).

Description of baseline characteristics according to quartiles of ascending aorta distensibility

Ascending aorta distensibility ranged between 1.13 and 16.15 $mmHg^{-1}.10^{-3}$ with a median of 5.88 $mmHg^{-1}.10^{-3}$ [IQ: 4.52 - 7.60]. Descending aorta distensibility ranged between 1.12 and 16.12 $mmHg^{-1}.10^{-3}$ with a median of 6.46 $mmHg^{-1}.10^{-3}$ [IQ: 5.16 - 7.84]. Clinical, angiographical and biological baseline characteristics according to quartile of ascending aorta distensibility are presented in **Table 1A.** Patients in the first quartile of ascending aorta distensibility – with the lowest aortic distensibility – were older than in the other quartiles (44.8 years in the first quartile versus 36.4 years in the fourth quartile, $p<0.001$). There was no difference in other cardiovascular risk factors according to the quartile of aorta distensibility.

Description of baseline characteristics according to quartiles of descending aorta distensibility

Patients in the first quartile of descending aorta distensibility – with the lowest aortic distensibility – were older (44.3 years old in the first quartile versus 36.9 years old in the fourth quartile, $p<0.001$). Patients with the lowest distensibility, in the first quartile, had more often diabetes mellitus (26.3% of patients in the first quartile versus 7.9% in individuals with preserved aortic distensibility in the fourth quartile, $p=0.003$). They also tended to have more often hypertension (26.3% of patients in the first quartile versus 13.1% in the fourth quartile, $p=0.057$) **(Table 1B).** Lengths of follow-up were similar according to quartile of ascending and descending aorta distensibility.

Table 1. Baseline characteristics according to quartile of ascending aorta distensibility (A) and to quartile of descending aorta distensibility (B)

A

	Overall	**Quartile of ascending aorta distensibility ($mmHg^{-1}.10^{-3}$)**				**p-value**
Quartile intervals ($mmHg^{-1}.10^{-3}$)	**(N=150)**	**Q1 [1.13 - 4.52] (N=38)**	**Q2 [4.53 - 5.87] (N=37)**	**Q3 [5.88 - 7.54] (N=37)**	**Q4 [7.62 - 16.15] (N=38)**	
Cardiovascular risk factors						
Age at first coronary event, median (IQR), y	42.7 [36.4 - 45.3]	44.8 [42.4 - 46.7]	42.3 [39.5 - 44.3]	42.1 [36.3 - 44.5]	36.4 [30.1 - 40.1]	<0.001
Age < 35 years	23 (15.3%)	1 (2.6%)	0 (0%)	5 (13.5%)	17 (44.7%)	<0.001
Women	18 (12.0%)	5 (13.2%)	5 (13.5%)	2 (5.4%)	6 (15.8%)	0.538
Family history of coronary artery disease	71 (47.3%)	18 (47.4%)	13 (35.1%)	16 (43.2%)	24 (63.2%)	0.099
BMI, median (IQR), kg/m^2	26.3 ± 4.2	26.1 ± 4.4	27.4 ± 4.6	25.8 ± 3.9	26.1 ± 3.8	0.443
Diabetes mellitus	18 (12.0%)	6 (15.8%)	5 (13.5%)	3 (8.1%)	4 (10.5%)	0.752
Hypertension	34 (22.7%)	10 (26.3%)	10 (27.0%)	9 (24.3%)	5 (13.2%)	0.439
Dyslipidemia	65 (43.3%)	17 (44.7%)	18 (48.6%)	17 (45.9%)	13 (34.2%)	0.605
Active smoking	77 (51.3%)	22 (57.9%)	20 (54.1%)	17 (45.9%)	18 (47.4%)	0.698
Comorbidities						
Chronic inflammatory disease*	10 (6.5%)	2 (5.2%)	3 (8.1%)	2 (5.4%)	3 (7.8%)	0.934
Ethnicity						
White European	104 (69.3%)	27 (71.0%)	28 (75.7%)	24 (64.9%)	25 (65.8%)	0.723
North Africa and Middle East	37 (24.7%)	10 (20.6%)	6 (16.3%)	12 (32.4%)	9 (26.9%)	0.332
Sub-Saharian Africa	3 (2.0%)	0 (0%)	1 (2.7%)	1 (2.7%)	1 (2.6%)	0.441
Asian continent	6 (0.4%)	1 (2.6%)	2 (5.4%)	0 (0%)	3 (7.9%)	0.792
Index presentation						
MI	134 (89.3%)	30 (78.9%)	34 (91.2%)	34 (91.2%)	36 (94.7%)	0.113
STEMI	101 (67.3%)	25 (65.8%)	21 (56.6%)	24 (64.9%)	31 (81.6%)	0.069
Stable angina	14 (9.3%)	7 (18.4%)	3 (8.1%)	2 (5.4%)	2 (5.3%)	0.158
Cardiac arrest	13 (8.7%)	3 (7.9%)	2 (5.4%)	3 (8.1%)	5 (13.1%)	-
LVEF (%)	55 ± 8	57 ± 7	55 ± 8	55 ± 8	55 ± 8	0.832
Angiographic characteristics						
1-vessel disease	97 (62.3%)	24 (63.2%)	23 (62.2%)	24 (64.9%)	26 (68.4%)	0.945
2-vessel disease	32 (20.6%)	9 (23.7%)	7 (18.9%)	9 (24.3%)	7 (18.4%)	0.937
3-vessel disease	17 (11.0%)	4 (10.5%)	5 (13.5%)	4 (10.8%)	4 (10.5%)	0.972
Multivessel disease***	48 (32.0%)	13 (34.2%)	12 (32.4%)	12 (32.4%)	11 (28.9%)	0.968

	Overall (N=150)	Q1 [1.13 - 4.52] (N=38)	Q2 [4.53 - 5.87] (N=37)	Q3 [5.88 - 7.54] (N=37)	Q4 [7.62 - 16.15] (N=38)	
Coronary revascularization						
PCI						0.318
Medical treatment	12 (11.3%)	2 (5.3%)	2 (5.4%)	7 (18.4%)	5 (13.5%)	0.318
CABG	0 (0%)	-	-	-	-	-
Biological results						
Haemoglobin (g/L)	14.5 ± 1.3	14.4 ± 1.6	14.5 ± 1.2	14.8 ± 1.1	14.5 ± 1.0	0.437
Platelets (/mm^3)	266 964 ± 78 130	236 500 ± 54 492	269 702 ± 48 797	262 824 ± 69 014	300 382 ± 114 884	0.024
Serum creatinine value (µmol/L)	72 [63 - 86]	71 [64 - 82]	67 [61 - 85]	77 [66 - 91]	73 [64 - 86]	0.421
LDL-c (g/L)	0.79 ± 0.40	0.74 ± 0.35	0.79 ± 0.37	0.88 ± 0.49	0.74 ± 0.38	0.499
HDL-c (g/L)	0.41 ± 0.11	0.46 ± 0.24	0.44 ± 0.14	0.41 ± 0.10	0.41 ± 0.11	0.875
HbA1c (%)	5.7 ± 1.1	5.6 ± 0.9	5.7 ± 0.8	5.9 ± 1.6	5.7 ± 1.2	0.605
Follow-up						
Follow-up (years)	3.0 [1.5 - 4.3]	3.1 [1.7 - 4.4]	2.6 [1.3 - 4.0]	3.3 [2.0 - 4.2]	2.7 [1.2 - 4.6]	0.571
Medication at cardiac MRI						
Beta blockers	115 (76.7%)	30 (78.9%)	27 (73.0%)	28 (75.7%)	30 (78.9%)	0.884
ARB/ACE inhibitors	100 (66.7%)	27 (71.1%)	22 (59.5%)	27 (73.0%)	25 (65.8%)	0.573
MRA	12 (8.0%)	2 (5.3%)	5 (%)	2 (5.4%)	3 (7.9%)	0.504
Calcium channel blockers	7 (4.7%)	3 (7.9%)	2 (5.4%)	1 (2.7%)	1 (2.6%)	0.694
Nitrates	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Aspirin	136 (90.7%)	36 (94.7%)	32 (86.5%)	34 (91.2%)	34 (89.5%)	0.547
P2Y12 inhibitor medication	114 (76.0%)	32 (84.2%)	30 (81.1%)	22 (59.5%)	30 (78.9%)	0.072

BP: Blood Pressure; MRI: Magnetic Resonance Imaging; BMI: Body Mass Index; MI: Myocardial Infarction; STEMI: ST segment Elevation Myocardial Infarction; LVEF: Left Ventricular Ejection Fraction; LM: Left Main; LAD: Left Anterior Descending; PCI: Percutaneaous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; MRA: Mineralocorticoid Receptor Antagonist; HbA1c: glycated haemoglobin

B

	Overall	Quartile of descending aorta distensibility ($mmHg^{-1}.10^{-3}$)				p-value
Quartile intervals ($mmHg^{-1}.10^{-3}$)	**(N=150)**	**Q1 [1.12 - 5.16] (N=38)**	**Q2 [5.17 - 6.45] (N=37)**	**Q3 [6.46 - 7.80] (N=37)**	**Q4 [7.81 - 16.12] (N=38)**	
Cardiovascular risk factors						
Age at first coronary event, median (IQR), y	42.1 [36.4 - 44.5]	44.3 [42.4 - 46.12]	42.3 [37.0 - 44.6]	41.2 [36.3 - 44.2]	36.9 [32.0 - 40.7]	<0.001
Age < 35 years	23 (15.3%)	1 (2.6%)	4 (10.8%)	5 (13.5%)	13 (34.2%)	0.001
Women	18 (12.0%)	2 (13.2%)	4 (10.8%)	7 (18.4%)	5 (13.1%)	0.333
Family history of CAD	71 (47.3%)	16 (42.1%)	14 (37.8%)	18 (48.6%)	23 (60.5%)	0.218
BMI, median (IQR), kg/m^2	26.3 ± 4.2	26.6 ± 3.7	27.5 ± 5.2	25.8 ± 3.9	25.6 ± 4.0	0.594
Diabetes mellitus	18 (12.0%)	10 (26.3%)	4 (10.8%)	0 (0%)	3 (7.9%)	0.003
Hypertension	34 (22.7%)	10 (26.3%)	9 (24.3%)	2 (5.4%)	5 (13.1%)	0.057
Dyslipidemia	65 (43.3%)	11 (28.9%)	12 (32.4%)	12 (32.4%)	11 (28.9%)	0.975
Active smoking	77 (51.3%)	18 (47.4%)	17 (45.9%)	21 (55.3%)	21 (56.8%)	0.72
Comorbidities						
Chronic inflammatory disease*	10 (6.5%)	1 (2.6%)	1 (2.7%)	3 (8.1%)	2 (5.3%)	0.639
Ethnicity						
White European	104 (69.3%)	28 (73.7%)	22 (59.5%)	28 (75.7%)	26 (68.4%)	0.432
North Africa and Middle East	37 (24.7%)	9 (23.7%)	13 (35.1%)	6 (16.2%)	9 (23.7%)	0.303
Sub-Saharian Africa	3 (2.0%)	0 (0%)	1 (2.7%)	1 (2.7%)	1 (2.6%)	0.792
Asian continent	6 (0.4%)	1 (2.6%)	1 (2.7%)	2 (5.4%)	2 (5.3%)	0.874
Index presentation						
MI	134 (89.3%)	31 (81.6%)	36 (97.3%)	33 (89.2%)	34 (89.5%)	0.182
STEMI	101 (67.3%)	26 (68.4%)	24 (64.9%)	22 (59.5%)	29 (76.3%)	0.168
Stable angina	14 (9.3%)	6 (15.8%)	1 (2.7%)	4 (10.8%)	3 (7.9%)	0.263
Cardiac arrest	13 (8.7%)	2 (13.2%)	6 (16.2%)	1 (2.7%)	4 (10.5%)	-
LVEF (%)	55 ± 8	56 ± 8	55 ± 6	56 ± 9	55 ± 8	0.587
Angiographic characteristics						
1-vessel disease	97 (62.3%)	24 (63.2%)	26 (70.3%)	20 (54.1%)	27 (71.1%)	0.384
2-vessel disease	32 (20.6%)	8 (21.1%)	8 (21.6%)	9 (24.3%)	6 (15.8%)	0.831
3-vessel disease	17 (11.0%)	4 (10.5%)	3 (8.1%)	6 (16.2%)	17 (44.7%)	0.727
Multivessel disease***	48 (32.0%)	12 (31.6%)	11 (29.7%)	15 (40.5%)	10 (26.3%)	0.594
Lesions per patient	1.4 ± 0.7	1.4 ± 0.8	1.4 ± 0.6	1.5 ± 0.8	1.3 ± 0.7	0.744
Coronary revascularization						
PCI	133 (88.7%)	34 (89%)	35 (95%)	31 (84%)	33 (87%)	0.406
Medical treatment	12 (11.3%)	2 (13.2%)	1 (2.7%)	5 (13.5%)	5 (13.1%)	0.406

Table 1 B – suite Quartile intervals ($mmHg^{-1}.10^{-3}$)	**Overall**	**Q1 [1.12 - 5.16]**	**Q2 [5.17 - 6.45]**	**Q3 [6.46 - 7.80]**	**Q4 [7.81 - 16.12]**	
	(N=150)	**(N=38)**	**(N=37)**	**(N=37)**	**(N=38)**	
Haemoglobin (g/L)	14.5 ± 1.3	14.6 ± 1.5	14.6 ± 1.2	14.4 ± 1.3	14.6 ± 1.1	0.639
Platelets (/mm^3)	266 964 ± 78 130	245 973 ± 60 969	280 294 ± 89 188	246 389 ± 57 279	298 265 ± 90 883	0.027
Serum creatinine value (µmol/L)	72 [63 - 86]	69 [64 - 81]	72 [63 - 79.0]	72 [62 – 91]	79 [68 – 88]	0.553
LDL-c (g/L)	0.79 ± 0.40	0.85 ± 0.36	0.77 ± 0.43	0.76 ± 0.40	0.78 ± 0.42	0.24
HDL-c (g/L)	0.41 ± 0.11	0.47 ± 0.25	0.41 ± 0.13	0.43 ± 0.12	0.43 ± 0.10	0.943
HbA1c (%)	5.7 ± 1.1	5.76 ± 1.05	5.59 ± 0.39	5.88 ± 1.74	5.71 ± 1.12	0.244
Follow-up						
Follow-up (years)	1.46/3.03/4.28 3.0+/-1.9	1.68/3.20/4.53 3.1+/-1.9	2.78/3.17/4.03 3.3+/-1.4	1.76/2.66/4.30 3.2+/-2.1	0.81/2.11/3.35 2.5+/-2.1	0.129
Medication at cardiac MRI						
Beta blockers	115 (76.7%)	30 (78.9%)	33 (89.2%)	33 (89.2%)	37 (97.4%)	0.091
ARB/ACE inhibitors	100 (66.7%)	30 (78.9%)	31 (83.8%)	30 (81.1%)	31 (81.6%)	0.962
MRA	12 (8.0%)	2 (13.2%)	4 (10.8%)	4 (10.8%)	4 (10.5%)	0.802
Calcium channel blockers	7 (4.7%)	6 (15.8%)	1 (2.7%)	1 (2.7%)	1 (2.6%)	0.034
Nitrates	0 (0%)	-	-	-	-	-
Aspirin	136 (90.7%)	34 (89.5%)	29 (78.4%)	31 (83.8%)	32 (84.2%)	0.633
P2Y12 inhibitor medication	114 (76.0%)	37 (97.4%)	36 (97.3%)	34 (91.9%)	37 (97.4%)	0.54

BP: Blood Pressure; MRI: Magnetic Resonance Imaging; BMI: Body Mass Index; MI: Myocardial Infarction; STEMI: ST segment Elevation Myocardial Infarction; LVEF: Left Ventricular Ejection Fraction; LM: Left Main; LAD: Left Anterior Descending; PCI: Percutaneaous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; MRA: Mineralocorticoid Receptor Antagonist; HbA1c: glycated haemoglobin

Association between MACE and aorta distensibility

Among the 150 patients of the study population, 24 (16%) presented at least one major adverse cardiac event with a rate of 5.3 per 100 patients-year. The median delay before the first MACE was 311 days from cardiac MRI.

Association between MACE and ascending aorta distensibility

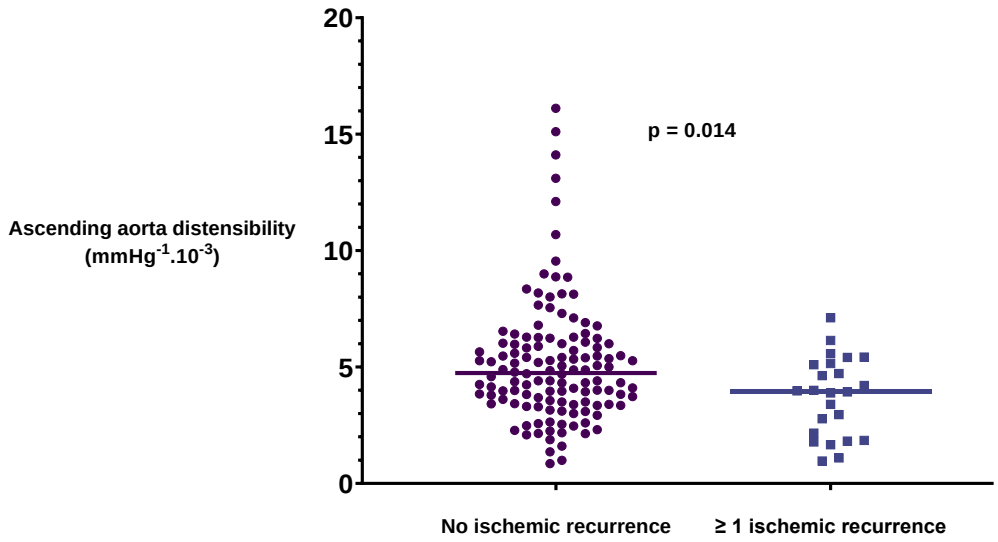
Ascending aorta distensibility was significantly lower in patients with at least one MACE compared with those who did not present MACE (respectively 5.27 [2.78 - 6.82] $mmHg^{-1}.10^{-3}$, versus 6.19 [4.67 - 7.94] $mmHg\text{-}1.10^{-3}$, p=0.02) **(figure 2A)**. Of note, there was no recurrent ischemic event in patients with preserved AAD above the value of 7 $mmHg.10^{-3}$. In multivariate analyses, after adjustment for age at MRI, active smoking and multivessel CAD at baseline, decreased ascending aorta distensibility remained significantly associated with MACE with an adjusted OR of 1.32 [1.02, 1.69] per decrease of 1 $mmHg^{-1}.10^{-3}$ **(Table 3).**

Association between MACE and descending aorta distensibility

There was no statistically significant association between a lower descending aorta distensibility and MACE (median descending aorta distensibility of 6.10 [4.92 - 7.01] $mmHg^{-1}.10^{-3}$ for patients who presented a MACE, versus 6.59 [5.24 - 8.13] $mmHg^{-1}.10^{-3}$ for the other, p=0.207) **(figure 2B).**

Figure 2. Ascending aorta distensibility (A) and Descending aorta distensibility (B) according to the occurrence of a recurrent ischemic event

(A)



(B)

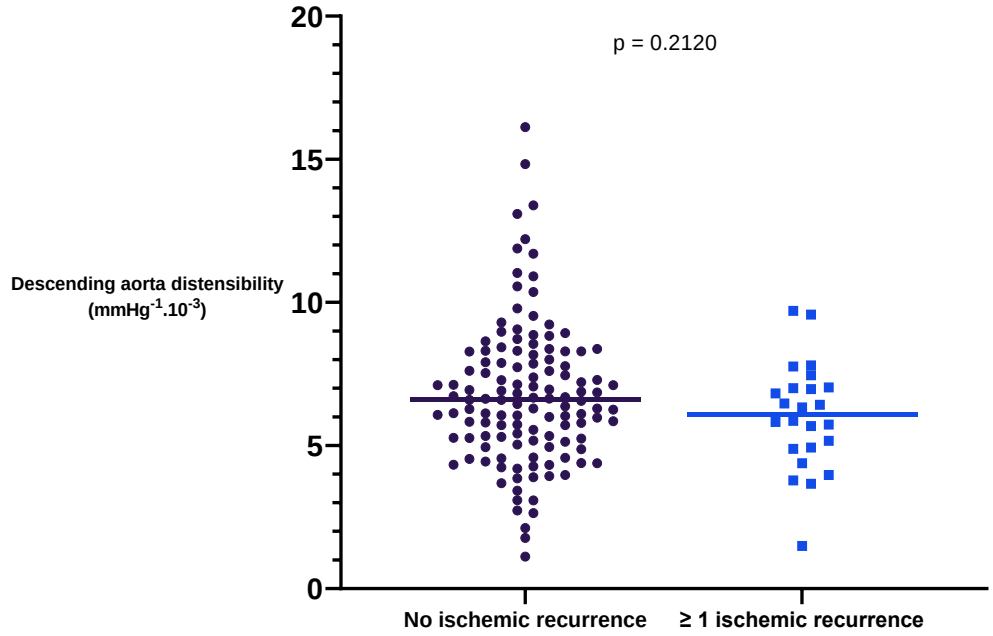


Table 3. Association between the decrease of ascending aorta distensibility and MACE in univariate and multivariate analyses

	Univariate		**Multivariate***	
	OR [CI95%]	**p**	**adjOR [CI95%]**	**p**
Decrease of ascending aorta distensibility (per decrease of 1 $mmHg^{-1}.10^{-3}$)	1.28 [1.05, 1.59]	0.009	1.32 [1.02, 1.69]	**0.028**
Age (per increase of 1 year)	1.1 [1, 1.21]	0.031	1.01 [0.90, 1.13]	0.893
Active smoking**	0.77 [0.32, 1.85]	0.556	0.67 [0.26, 1.76]	0.425
Multivessel coronary artery disease***	3.79 [1.54, 9.33]	0.004	3.91 [1.49, 10.29]	**0.005**

*Note: adjustment variables = age at MRI, active smoking and multivessel CAD at baseline

** active smoking at inclusion

*** ≥ 2 coronary arteries diseased

DISCUSSION

The present study assesses the association between proximal aortic distensibility measured with MRI using central pressures and the prognosis of premature CAD. Our observations demonstrate that the measure of proximal aortic distensibility with MRI is an efficient tool to stratify the risk and prognosis of individuals with premature coronary artery disease. The results of this study are consistent with those observed in the MESA study evaluating aortic distensibility and outcomes in patients aged 45 years or more (87).

Developing new risk markers of premature CAD is an important objective, as current guidelines and algorithm are unable to identify and treat the vast majority of individuals at risk of myocardial infarction at a young age. Indeed, using simple clinical risk factors and biomarkers, only one out of two individuals less than 55 years old who presented a MI was eligible to statin therapy in primary prevention according to American guidelines, with a similar observation with European Guidelines (139, 140). The added value of aortic MRI as a reflect of cardiovascular health and factor of potential future outcomes is paramount in this young population with a compromised cardiovascular prognosis. Of note, in the MESA, ascending aortic distensibility could independently predict incident MACE on top of CAC score, carotid intima-media thickness and the ankle-brachial pressure index, offering the possibility to provide a multimodal assessment of cardiovascular risk.

The present observations raise the question whether aortic distensibility could become a target goal to measure the impact of cardiovascular risk control by lifestyle changes and treatments. For instance, in a cohort study of 138 participants with a baseline sedentary lifestyle willing to train for a marathon, physical training was associated with a reduced central blood pressure and descending aorta (10). Thus, proximal aortic distensibility may serve at a given point in a lifetime as an integrated measure of cardiovascular risk as it reflects the mechanical

effects of aging on a given individual aortic wall with specific constitutional properties as well as the detrimental effects of cardiovascular risk factors.

Cardiac MRI is noninvasive, reproducible and routinely feasible in daily practice, especially as MRI is recommended in European and American guidelines for detection of myocardial ischemia (11, 12). Ascending aorta distensibility could be added to further biomarkers aiming to better evaluate the residual cardiovascular risk such as hypersensitive C-reactive protein concentration (202, 203). Whether inflammation or abnormal cholesterol efflux capacity play a role in the loss of aorta distensibility is another question that should be investigated to provide a more inclusive and translational outlook on cardiovascular risk stratification. For instance, reduced proximal aorta distensibility was observed in patients with chronic inflammatory disease (204). Even more interestingly, in healthy individuals, the measure of inflammation biomarkers was also associated with proximal aorta stiffness, offering a new pathway to integrate from between inflammation, atherosclerosis and vascular dysfunction (205).

Study limitations

These results were obtained on 150 patients, which is a small effective to study a biomarker in CAD, although it is quite large for a first study on MRI and about this issue. Diabetes mellitus and ethnicity were not included in the multivariate analyses because of a small effective, although these factors are associated with occurrence of ischemic events in larger registries (3, 4). Follow-up durations are inhomogeneous between patients, which exposes to a follow-up bias. However, there was no difference in follow-up duration between patients who presented a MACE and those who had not.

CONCLUSIONS

Altered ascending aorta distensibility measured by MRI was associated to a worse prognosis defined by the occurrence of at least one MACE in patients who were diagnosed for CAD before the age of 45 years. No association was found for descending aorta distensibility. These results encourage to pursue research about the use of this biomarker in premature coronary artery disease either for risk stratification at diagnosis or even as a modifiable

6.Guideline Performance in Detection and Treatment of Young Patients with Premature Myocardial Infarction

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ABSTRACT

BACKGROUND: The 2018 AHA/ACC cholesterol guideline changed statin eligibility criteria for primary prevention to include multiple "risk enhancers" and novel intensive lipid-lowering therapies for secondary prevention.

OBJECTIVES: To determine how guideline changes impacted identification for preventive therapy in young adults with premature myocardial infarction (MI).

METHODS: We identified adults presenting with first MI at Duke Hospital. Eligibility for statin therapy at the time of index MI was determined using both the 2013 and 2018 AHA/ACC guidelines criteria. We also determined potential eligibility for intensive lipid-lowering therapies (very high risk) under the 2018 AHA/ACC guidelines. We assessed the composite of all-cause death, recurrent MI, or stroke rates in adults considered "very high risk" vs. not.

RESULTS: Among 6,639 MI patients, 41% were <55 years ("younger"), 35% were 55–65 ("middle-aged"), and 24% were 66–75 ("older"). Younger adults were more frequently smokers (52% vs. 38% vs. 22%), obese (42% vs. 34% vs. 31%), with metabolic syndrome (21% vs. 19% vs. 17%), and higher LDL-C (117 vs. 107 vs. 103 mg/dL); p-trend <0.01 for all. Pre-MI, fewer younger adults met guideline indications for statin therapy than middle-aged and older adults. The 2018 guideline identified fewer younger adults eligible for statin therapy at the time of their MI than the 2013 guideline (46.4% vs. 56.7%, p<0.01). Younger patients also less frequently met very high-risk criteria for intensive secondary prevention lipid-lowering therapy (28.3% vs. 40.0% vs. 81.4%, p<0.01). Over a median 8 years of follow-up, very high-risk criteria were associated with increased risk of major adverse cardiovascular events in individuals <55 years (HR 2.09, 95% CI 1.82–2.41, p<0.001), as was the case in older age groups (p-interaction=0.54).

CONCLUSIONS: Most younger patients with premature MI are not identified as statin candidates prior to their event based on the 2018 guidelines and most with premature MI are not recommended for intensive post-MI lipid management.

ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	atherosclerotic cardiovascular disease
DDCD	Duke Databank for Cardiovascular Disease
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction

INTRODUCTION

Lipid-lowering therapies are a cornerstone of both primary and secondary prevention of cardiovascular disease (126, 206). Previous guidelines for cholesterol management expanded statin treatment eligibility based on 10-year atherosclerotic cardiovascular disease (ASCVD) risk score (57, 207–210), but because this score is highly age-dependent, guidelines often failed to identify young patients at risk for premature coronary artery disease (CAD) (109, 138, 141). The identification of those at risk for premature CAD is of increasing importance since young individuals represent a growing portion of the ischemic heart disease population (73). Adults who develop CAD early in life experience a poor overall long-term prognosis with frequent premature death, multiple ischemic recurrences, and rapid evolution towards multivessel disease, thereby highlighting the importance of early primary detection and aggressive early secondary prevention (121).

The more recent 2018 American College of Cardiology (ACC) and American Heart Association (AHA) Multisociety Guideline on the Management of Blood Cholesterol provided new criteria to enable a more tailored risk assessment to guide statin prescription in primary prevention (126). Multiple risk enhancers were included among the new criteria, including chronic inflammatory disorders, high-risk ethnic groups, and premature menopause (121). The 2018 guideline also updated secondary prevention lipid recommendations, including recommendations for non-statin lipid-lowering therapies such as ezetimibe and PCSK9 inhibitors as part of the treatment strategy among myocardial infarction (MI) patients at the highest risk for recurrent ASCVD events (141).

The objectives of this study were to determine: 1) how often lipid guidelines would have recommended statin therapy among those who develop premature CAD; 2) how often intensive post-MI lipid-lowering management is recommended in younger patients; and 3) whether current

criteria used to identify those at highest risk in secondary prevention actually identify higher risk similarly across age groups.

METHODS

Study Design and Study Population

The Duke Databank for Cardiovascular Disease (DDCD) is a prospective registry with a pre-specified data collection of clinical and angiographic baseline characteristics of all patients who underwent cardiac catheterization at Duke University Medical Center. In the DDCD, death and cardiovascular events are followed via annual surveys in all patients with significant CAD (122). When patients are hospitalized at Duke hospital, the events are reported by physicians and ascertained from Duke Health System records. Follow-up calls and mailed surveys are sent at 6 and 12 months after the index catheterization and then annually thereafter to collect events occurring outside of Duke Hospital. Hospitalization events reported on follow-up surveys occurring at outside hospitals were classified by an events committee, who reviewed information reported by the patient and medical records acquired from the admitting hospital (211). For patients lost to follow-up, a query of the National Death Index was obtained to ascertain vital status through 2014.

Using the DDCD, we included patients previously free of cardiovascular disease who were admitted from 1995 to 2012 for a first acute MI with angiographic findings of obstructive ASCVD. MI was ascertained at the time of cardiac catheterization based on the hospitalization record. Clinical variables for the patients were collected at the time of admission including age, race, body mass index, cardiovascular risk factors and blood pressure. Other historical variables were collected in the databank using data from the patient medical record prior to the admission including medication prior to MI, history of COPD and dialysis. This time period (1995-2012) was chosen to allow for adequate outcome assessment post-first MI event. Obstructive CAD was defined as a coronary stenosis ≥50 %. Patients with missing blood cholesterol values at the time

of or within +/- 1 year of the index catheterization were excluded. In order to identify adults who were previously free of ASCVD, patients with prior documented stroke, MI, peripheral artery disease, or obstructive CAD were excluded.

This retrospective observational study was approved by the Duke Institutional Review Board under a waiver of informed consent and Health Insurance Portability and Accountability Act of 1996 approval. This analysis was approved by the Duke University Health System IRB (PRO 00102546).

Clinical characteristics of adults with obstructive CAD

Baseline clinical and catheterization variables for each patient are collected and registered prospectively at the time of catheterization using pre-specified methods in the DDCD (122, 125, 211). These baseline variables included cardiovascular risk factors, medical and cardiovascular history prior to the index catheterization, and angiographic results. Baseline laboratory measures were ascertained from the DDCD intake form supplemented by a search of the patient's electronic medical record and were based on the value recorded at catheterization intake or the most recent value within 365 days prior. If no prior measure was available, then the earliest value within the subsequent 365 days was used. Baseline medication use was ascertained from the DDCD intake form, as well as a search of the patient's medical record. Medication use was defined as any prescription record prior to the current hospital admission and within 365 days prior to catheterization.

Among these variables, active smoking, diabetes, hypertension, dyslipidemia, and familial history of CAD, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were used to evaluate participants' 10-year ASCVD risk score and lifetime risk prior to their index MI. The 10-year ASCVD score was calculated using the pooled cohort equations in those 40 to 79 years old, and lifetime risk was assessed per Berry et al. in those older than 20 years (212). The following risk enhancers included in the 2018

ACC/AHA Guidelines for Blood Cholesterol were collected using the DDCD history and physical intake examination forms: connective tissue disease, premature menopause (before 40 years old), family history of CAD, ethnicity, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), estimated glomerular filtration rate <60 ml/min, and metabolic syndrome. At least 3 of the following criteria needed to be present to meet the definition of metabolic syndrome: body mass index ≥30 kg/m^2, baseline triglycerides ≥175 mg/dL, baseline HDL-C <40 mg/Dl for men and <50 mg/Dl for women, hypertension or on an anti-hypertensive drug, and diabetes. HIV status was not collected at the time of catheterization and, therefore, was derived using a search of the patient's electronic medical record prior to catheterization. Asian ethnicity was used as a surrogate for South Asian ethnicity.

Continuous variables are presented as median and interquartile ranges and compared across age categories using p-values for trend: Cochrane-Armitage Trend test for binary variables, Cochran-Mantel Haenszel test for categorical variables, and Spearman Correlation test for continuous variables. Descriptive summaries of the cohort and risk factors are based on available data with missing values excluded from calculations **(Online Figure 1**).

Primary prevention statin eligibility

The objective of this analysis was to identify the proportion of adults who would have qualified for a statin prior to their first MI according to each age category: <55 years, 55–65 years, and 66–75 years. Using individuals' risk profile at the time of their first MI, we identified those eligible for statin therapy in primary prevention based on a class I or a class IIa recommendation in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults and the 2018 ACC/AHA Multi-society Guideline on the Management of Blood Cholesterol, respectively.

Eligibility for statins in primary prevention was defined as having a class I or IIa recommendation. The criteria for eligibility for statins according to 2013 and 2018 guidelines

are listed in **Online Table 1**. For both the 2013 and 2018 guidelines, individuals with LDL-C ≥190 mg/Dl have a class I recommendation for statins, as well as diabetics with an LDL-C higher than 70 mg/Dl. The 2013 guideline provided a class I recommendation for statins for non-diabetic individuals with a 10-year ASCVD score ≥7.5%. This recommendation was modified by the 2018 guideline, raising the ASCVD risk to 20% or more to be class I eligible, or higher than 7.5% combined with a risk enhancer. Patients with an ASCVD score higher than 7.5% without a risk enhancer became eligible for statins (class IIa recommendation). Previous class IIa recommendation for statins in individuals with a 5–7.5% 10-year ASCVD score in the 2013 ACC/AHA guideline was downgraded to a class IIb in the 2018 guideline and, therefore, considered as non-eligible in the following analysis. Eventually, the 2018 guideline established an additional class IIa recommendation for statins in young adults 20–39 years with a combination of LDL-C ≥160 mg/Dl and a risk enhancer. Patients already treated with statins prior to MI (2.7%) were considered as eligible according to both guidelines. The list of risk enhancers considered in the 2018 ACC/AHA guideline and available in the DDCD is displayed in **Online Table 3.**

Individuals with a weak recommendation (class IIb) were not considered as eligible for statins in the primary analysis. However, the proportion of adults meeting IIb recommendations were evaluated. This included adults with 10-year risk between 5-7.5% and one risk enhancer and adults with LDL-C ≥160 mg/Dl and <190 mg/Dl without a risk enhancer **(online table 1).**

We compared the sensitivity of the 2013 vs. 2018 ACC/AHA guideline based on their ability to identify patients for statin therapy prior to their event using the homogeneity test. In order to evaluate the performance of the 2013 and 2018 guidelines, we excluded 252 patients (3.8%), due to missing data for systolic BP. To allow for inferences of results to the entire cohort, inverse probability weighting was used to adjust summary statistics and p-values.

Guideline Recommendations for Secondary Prevention : Assessment of "very high risk"

The 2018 ACC/AHA guidelines recommend consideration of PCSK9 inhibitor therapy for those at "very high risk" of events who have uncontrolled LDL-C, despite statin and ezetimibe therapy (Class IIa). We assessed the proportion of patients who would be considered "very high risk" after their first event and, consequently, potentially eligible for PCSK9 inhibitor therapy if LDL-C levels remained elevated. Very high-risk status for future ASCVD was defined as two or more of the following criteria: age ≥65 years, diabetes, hypertension, glomerular filtration rate of 15–59 mL/min/1.73m^2, current smoking, or history of heart failure. We evaluated the association between presence or absence of very high-risk criteria and the time from catheterization to the composite of all-cause death, non-fatal recurrent MI, or stroke across age. Patients were followed until 8 years after the index MI, or through the end of DDCD follow-up in December 2014.

We evaluated the cumulative incidence of the composite of stroke, MI, or all-cause mortality stratified by age group in adults considered at "very high risk" and "not at very high risk" using Kaplan-Meier analyses, with cumulative incidence curves through 8 years of follow-up compared using the log-rank test. Heterogeneity in the association between very high-risk criteria and subsequent events across age groups was evaluated by testing for a significant interaction between these factors in a Cox regression model for time-to-first event. All statistical analyses were performed using SAS software, Version 9.4, SAS Institute, Inc. (Cary, NC, USA).

RESULTS

Baseline Characteristics.

Among 6,639 patients receiving cardiac catheterization who were admitted for a first MI with obstructive CAD, 41% were aged <55 years (n=2733), 35% were 55–65 years (n=2324), and 24% were 66–75 (n=1582). The selection of patients for this study is displayed in **Online Figure 1 and online table 2.** Baseline characteristics are displayed in **Table 1.** Compared with

older and middle-aged adults, younger adults with MI were more frequently male (75.8% vs. 70.8% vs. 58.1%, p <0.001), African-American (25.2% vs. 21.2% vs. 21.1%, p<0.001), smokers (51.8% vs. 38.3% vs. 21.6%, p<0.001), and had higher levels of LDL-C and triglycerides. Conversely, individuals <55 years old less frequently had hypertension (46.5% vs. 56.6% vs. 63.9%, p<0.001) and diabetes (18.9% vs. 24.2% vs. 28.6%, p<0.001).

Atherosclerotic Cardiovascular Disease Score and Risk Enhancers

Among younger patients (<55 years), 431 (15.8%) individuals were aged less than 40 years-old and thus could not have an evaluation of the 10-year ASCVD score. Among younger patients (<55 years), the 10-year ASCVD score could only be evaluated in those 40–54 years of age (84.3%). Younger individuals had a lower 10-year ASCVD risk score (median risk of 6.4% vs. 11.6% vs. 19.6%, p<0.001) calculated prior to their index MI compared with older and middle-aged patients, but a greater lifetime risk (median risk of 33.9% vs. 32.2% vs. 31.9%, p<0.001) (**Table 2**). Obesity, metabolic syndrome, high triglycerides, and familial history of CAD were more frequent among young patients admitted with premature MI than the other age categories. Conversely, chronic kidney disease was more frequent among older categories of patients (**Table 2**).

Table 1. Baseline Characteristics at Admission for a First MI According to Age Category

	18 ≤ Age <55 (N=2733)	55 ≤ Age ≤65 (N=2324)	65< Age ≤75 (N=1582)	All (N=6639)	P-value for trend
Demographics and risk factors					
Age at catheterization, years	48 (43 - 51)	60 (57 - 63)	70 (68 - 73)	57 (50 - 65)	
Female	661 (24.2%)	676 (29.1%)	663 (41.9%)	2000 (30.1%)	<.001
Race					**<.001**
White	1780 (65.8%)	1645 (71.6%)	1133 (72.8%)	4558 (69.5%)	
Black African	681 (25.2%)	488 (21. 2%)	329 (21.1%)	1498 (22.8%)	
Asian	22 (0.8%)	26 (1.1%)	9 (0.6%)	57 (0.9%)	
American Indian	165 (6.1%)	98 (4.3%)	62 (4.0%)	325 (5.0%)	
Native Hawaiian	2 (0.1%)	1 (0.0%)	1 (0.1%)	4 (0.1%)	
Other	56 (2.1%)	40 (1.7%)	23 (1.5%)	119 (1.8%)	
BMI (kg/m^2)	29 (26 - 33)	28 (25 - 32)	27 (24 - 31)	28 (25 - 32)	<.001
BMI categories					<.001
BMI <25	520 (19.2%)	561 (24.3%)	479 (30.4%)	1560 (23.6%)	
25 ≤ BMI <30	1066 (39.3%)	971 (42.0%)	609 (38.7%)	2646 (40.1%)	
30 ≤ BMI ≤35	694 (25.6%)	467 (20.2%)	295 (18.7%)	1456 (22.1%)	
BMI >35	434 (16.0%)	311 (13.5%)	191 (12.1%)	936 (14.2%)	
History of smoking					<.001
Never	1080 (39.5%)	1112 (47.8%)	978 (61.8%)	3170 (47.7%)	
Former	236 (8.6%)	321 (13.8%)	262 (16.6%)	819 (12.3%)	
Current	1417 (51.8%)	891 (38.3%)	342 (21.6%)	2650 (39.9%)	
History of hypertension	1271 (46.5%)	1316 (56.6%)	1011 (63.9%)	3598 (54.2%)	<.001
History of diabetes	517 (18.9%)	562 (24.2%)	452 (28.6%)	1531 (23.1%)	<.001
History of hyperlipidemia	1093 (40.0%)	1020 (43.9%)	715 (45.2%)	2828 (42.6%)	<.001
History of COPD	60 (2.2%)	70 (3.0%)	72 (4.6%)	202 (3.0%)	<.001
Patient currently on dialysis	22 (0.8%)	27 (1.2%)	22 (1.4%)	71 (1.1%)	0.062
History of liver disease	8 (0.3%)	8 (0.3%)	3 (0.2%)	19 (0.3%)	0.619
Reason for admission					<0.001
STEMI	1980 (72.4%)	1480 (63.7%)	926 (58.5%)	4356 (66.1%)	
NSTEMI	698 (25.5%)	785 (33.8%)	582 (36.8%)	2065 (31.1%)	
MI unspecified	55 (2.0%)	59 (2.5%)	74 (4.7%)	188 (2.8%)	
Number of significantly diseased vessels					**<.001**
One	1512 (55.3%)	1038 (44.7%)	587 (37.1%)	3137 (47.3%)	
Two	738 (27.0%)	676 (29.1%)	476 (30.1%)	1890 (28.5%)	
Three	483 (17.7%)	610 (26.2%)	519 (32.8%)	1612 (24.3%)	

Table 1 - suite	**18 ≤ Age <55 (N=2733)**	**55 ≤ Age ≤65 (N=2324)**	**65< Age ≤75 (N=1582)**	**All (N=6639)**	**P-value for trend**
Laboratory values*					
Triglycerides baseline value	123 (82 - 181)	112 (75 - 169)	101 (66 - 149)	114 (75 - 170)	<.001
Total cholesterol baseline value	183 (157 - 215)	175 (148 - 203)	167 (142 - 197)	177 (150 - 207)	<.001
HDL baseline value	37 (31 - 44)	39 (33 - 47)	41 (34 - 49)	39 (32 - 47)	<.001
HDL<40 mg/dL for men,<50 for women	1808 (66.2%)	1437 (61.8%)	945 (59.7%)	4190 (63.1%)	<.001
LDL baseline value	117 (91 - 143)	107 (84 - 133)	103 (79 - 128)	110 (85 - 136)	<.001
LDL category					<.001
LDL <70	259 (9.5%)	312 (13.4%)	254 (16.1%)	825 (12.4%)	
70 ≤ LDL <100	624 (22.8%)	646 (27.8%)	492 (31.1%)	1762 (26.5%)	
100 ≤ LDL <130	816 (29.9%)	718 (30.9%)	463 (29.3%)	1997 (30.1%)	
130 ≤ LDL <190	897 (32.8%)	584 (25.1%)	325 (20.5%)	1806 (27.2%)	
LDL ≥190	137 (5.0%)	64 (2.8%)	48 (3.0%)	249 (3.8%)	
LDL≥160	422 (15.4%)	238 (10.2%)	132 /(8.3%)	792 /(11.9%)	<0.001
Systolic BP (mmHg)	129 (115 - 144)	132 (117 - 149)	136 (118 - 154)	131 (117 - 148)	<.001
Diastolic BP (mmHg)	79 (70 - 90)	78 (68 - 88)	75 (66 - 84)	78 (68 - 88)	<.001
Heart rate (bpm)	74 (64 - 85)	74 (63 - 85)	73 (64 - 86)	73 (64 - 85)	0.583
Medications prior to MI†					
Hypertension treatment	190 (7.0%)	228 (9.8%)	174 (11.0%)	592 (8.9%)	<.001
Aspirin	132 (4.8%)	154 (6.6%)	107 (6.8%)	393 (5.9%)	0.004
Statin	74 (2.7%)	87 (3.7%)	74 (4.7%)	235 (3.5%)	<.001

*Baseline laboratory measures are based on the value recorded at catheterization intake or the most recent value within 365 days prior. If no prior measure was available, then the earliest value within the next 365 days was used.

†Baseline medication use was determined by any prescription record prior to the current hospital admission and within 365 days prior to catheterization.

BMI = body mass index; BP = blood pressure; bpm = beats per minute; COPD = chronic obstructive pulmonary disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction

Table 2. Risk Enhancers According to Age Groups

	18 ≤ Age <55 (N=2733)	55 ≤ Age ≤65 (N=2324)	65 < Age ≤75 (N=1582)	All (N=6639)	P-value for trend
Risk enhancers					
Family history of CAD	919 (33.6%)	622 (26.8%)	344 (21.7%)	1885 (28.4%)	<.001
Metabolic syndrome	573 (21.0%)	432 (18.6%)	273 (17.3%)	1278 (19.2%)	0.002
eGFR mL/min <60%	199 (7.4%)	409 (17.8%)	569 (36.3%)	1177 (17.9%)	<.001
Menopause <40 years old	24 (3.6%)	34 (5.0%)	28 (4.2%)	86 (4.3%)	0.596
Body mass index ≥30	1128 (41.6%)	778 (33.7%)	486 (30.9%)	2392 (36.3%)	<.001
HIV/AIDS	16 (0.6%)	5 (0.2%)	0 (0.0%)	21 (0.3%)	<.001
History of connective tissue disease	10 (0.4%)	3 (0.1%)	1 (0.1%)	14 (0.2%)	0.026
Asian ethnicity	22 (0.8%)	26 (1.1%)	9 (0.6%)	57 (0.9%)	0.598
Triglycerides ≥175 mg/dL	754 (27.6%)	537 (23.1%)	258 (16.3%)	1549 (23.3%)	<.001
Number of risk enhancers					0.026
0 risk enhancer	725 (26.5%)	750 (32.3%)	462 (29.2%)	1937 (29.2%)	
1 risk enhancer	1024(37.5%)	805 (34.6%)	584 (36.9%)	2413 (36.3%)	
2 risk enhancers	511 (18.7%)	407 (17.5%)	303 (19.2%)	1221 (18.4%)	
≥3 risk enhancers	473 (17.3%)	362 (15.6%)	233 (14.7%)	1068 (16.1%)	
Risk scores					
10-year ASCVD risk, %					<.001
N*	2302	2230	1526	6058	
Median (25th, 75th)	6.4 (3.7, 10.4)	11.6 (7.3, 17.2)	19.6 (13.4, 28.4)	10.9 (6.0, 18.2)	
Lifetime risk, %					<.001
N	2717	2312	1566	6595	
Median (25th, 75th)	33.9 (29.2, 39.6)	32.2 (29.4, 38.2)	31.9 (29.3, 37.2)	32.2 (29.3, 38.7)	

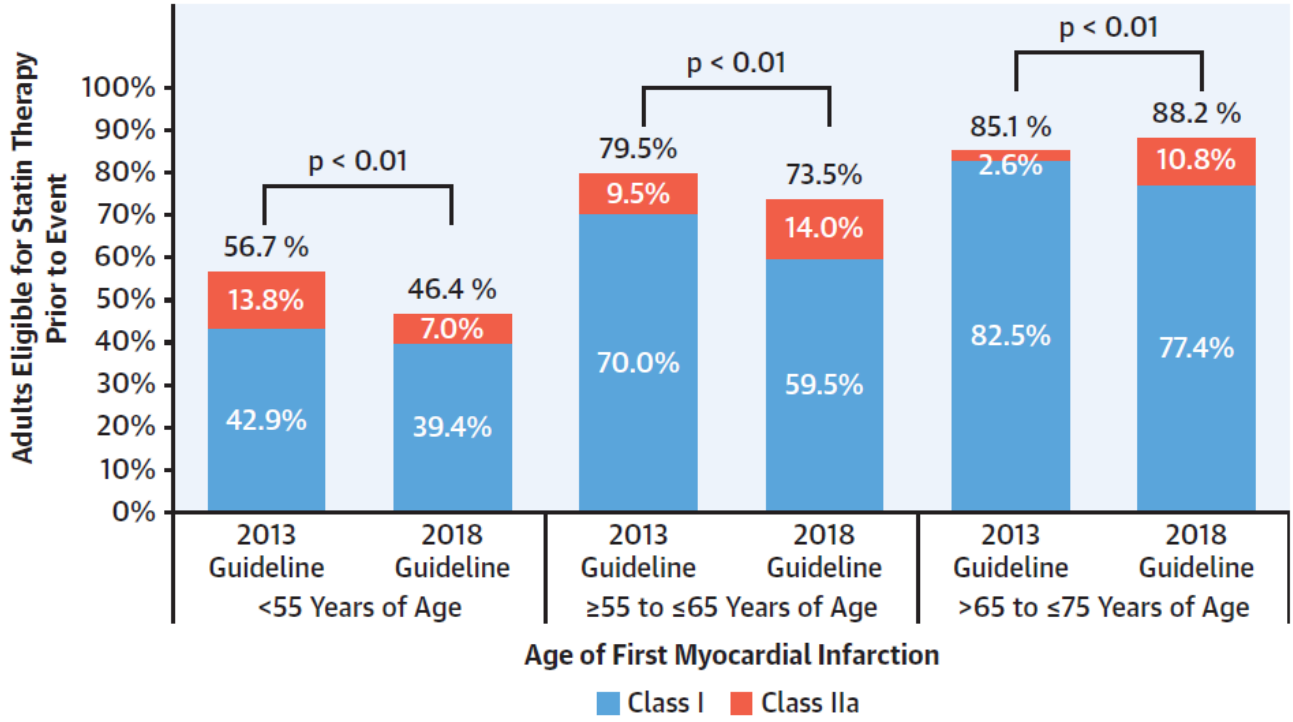
*10-year ASCVD risk score only calculated among patients ≥40 years old

ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; eGRF = estimated glomerular filtration rate; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome

Eligibility for primary prevention statin

Prior to their first MI, younger adults were less likely to meet a guideline class I recommendation for statins under the 2013 guideline (42.9 % vs. 70.0% vs. 82.5%, p <0.001) and the 2018 guideline (39.4% vs. 59.5% vs 77.4%, p <0.001). When taking into account both class I and class IIa recommendations, individuals aged <55 years were less likely to be eligible for statins prior their index MI under both the 2013 (56.7% vs. 79.5%, 85.2%, p < 0.01) and 2018 guidelines (46.4% vs. 73.5% vs. 88.2%, p <0.01) (**Central Illustration**). Compared with 2013, the 2018 guideline would have identified fewer young adults for statin therapy prior to their first MI (46.4% vs. 56.7%, p<0.01). **Online Table 4** shows the proportion of adults by age group who met a class IIb recommendations for statins. Of those in the younger age group, 6.2 % had a 10-year ASCVD risk score between 5 – 7.5 % with a risk enhancer (class IIb recommendation for primary prevention statins), which was higher than the proportion in older age categories (p<0.001). A smaller number (1.3%) had an LDL-C between 160 mg/dL and 190 mg/dL without a risk enhancer, which was also higher than the proportion of older adults who met these criteria (p<0.001).

CENTRAL ILLUSTRATION **Performance of the 2013 and 2018 Cholesterol Guidelines of the American College of Cardiology and American Heart Association**



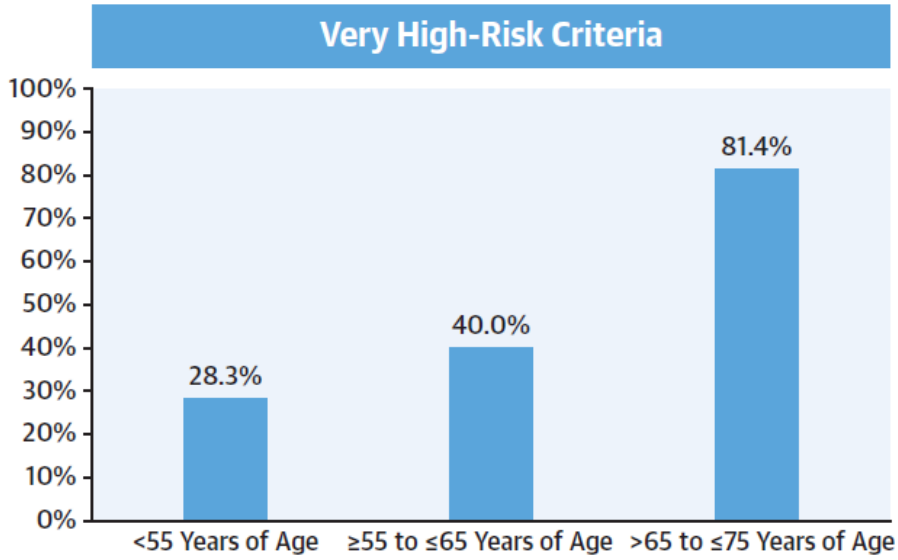
Zeitouni, M. et al. J Am Coll Cardiol. 2020;76(6):653-64.

Performance of the 2013 and 2018 cholesterol guidelines of the American College of Cardiology and American Heart Association to assign primary prevention statin treatment to individuals with incident myocardial infarction according to age groups.

Performance of "very high risk" criteria across age groups

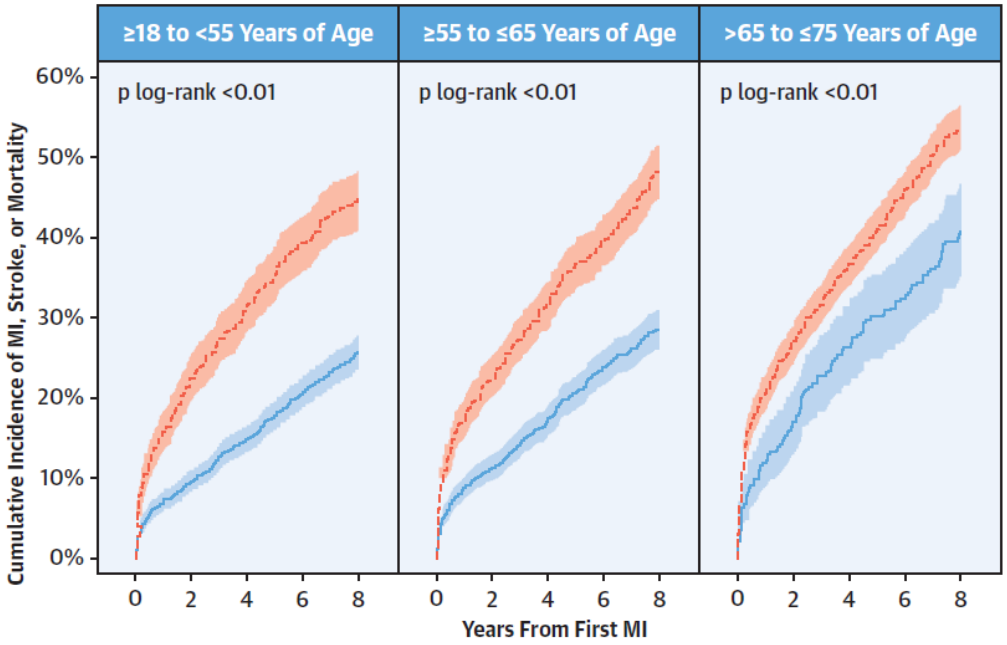
Subsequent to their first MI, only one in four young patients (28.3%) met the very high-risk criteria compared with 40.0% of middle-aged and 81.4% of older patients (p-trend<0.001) (**Figure 1**). During 8 years of follow-up, patients with very high-risk criteria according to the 2018 guideline had a twice higher rate of death, non-fatal MI, or stroke compared with other patients (hazard ratio [HR] 2.15, 95% confidence interval [CI] 1.98–2.33, p<0.001); this finding was driven by the event of all-cause death (36.1% vs. 14.1%, p<0.01). The association between very high-risk criteria and time to subsequent major adverse cardiovascular events was consistent across age groups (p-interaction=0.54, **Online Figure 2**). Younger patients with very high-risk criteria were at higher risk of all-cause death, MI, or stroke compared with those without these criteria (44.6% vs. 25.9%, HR 2.09, 95% CI 1.82–2.41, p<0.001). These observations were consistent (p=0.53) among patients aged 55–65 years old (48.1% vs. 28.5%, HR 1.97, 95% CI 1.72–2.27, p<0.001) and 66–75 years (53.6% vs. 40.8%, HR 1.51, 95% CI 1.23–1.84, p<0.001) (**Figure 2**).

FIGURE 1 Eligibility for Nonstatin Lipid-Lowering Therapies



Eligibility for nonstatin lipid-lowering therapies according to the 2018 guidelines of the American College of Cardiology and the American Heart Association by age groups.

FIGURE 2 Association Between Nonstatin Lipid-Lowering Therapies and Death, MI, or Stroke



At Risk															
-- Very High-Risk	1,959	1,773	1,556	1,331	1,109	1,394	1,238	1,060	903	732	295	246	207	167	135
— Not Very High-Risk	774	602	487	379	303	930	720	569	447	342	1,287	946	751	597	451

Association between eligibility for nonstatin lipid-lowering therapies for secondary prevention and death, myocardial infarction (MI), or stroke across age groups.

DISCUSSION

The 2018 ACC/AHA guideline incorporated a number of updates relative to prior guidelines, including more personalized criteria to identify candidates for statins for primary prevention, as well as a new risk stratification concept to guide the intensity of lipid-lowering in secondary prevention. We sought to determine how these guideline changes affected potential therapy recommendations for adults who develop premature ischemic heart disease. We found that approximately half of adults who developed premature CAD would have failed to meet a statin recommendation prior to their first event, and with fewer adults identified using the 2018 guideline criteria compared with 2013. As age increased, the proportion of adults with incident ischemic heart disease that would have been eligible for statin therapy prior to the onset of their event increased. Additionally, we note that after their first MI, far fewer younger individuals would be eligible for the most intensive lipid-lowering therapies for secondary prevention compared with older adults.

To our knowledge, this is among the first studies to comprehensively evaluate statin guideline eligibility with a focus on premature heart disease since the release of the most recent cholesterol guideline and implementation of risk enhancers. Previous studies have demonstrated that older cholesterol guidelines frequently failed to assign primary prevention statins to young individuals at risk of acute MI (109, 138). Our results demonstrate that the situation has not improved under the 2018 guideline, with more than 50% of young patients not eligible for statins prior to their acute MI. In contrast, more than 90% of older adults presenting with their first MI would have been recommended for statin therapy prior to their event. This failure to detect young patients at risk occurs despite these young patients having a higher prevalence of cardiovascular risk factors compared with their older counterparts, including higher rates of smoking, obesity, high LDL-C, and low HDL-C.

By providing risk enhancers specific to young patients at risk of premature CAD, the 2018 ACC/AHA guideline had the potential to improve risk identification. Many of these risk enhancers, such as obesity and metabolic syndrome, are described as strong correlates of poor cardiovascular outcomes and premature cardiovascular death among middle-aged American adults (128–130). Nevertheless, the 2018 guideline identified fewer younger patients for statin therapy than the 2013 guideline. There are several potential explanations for the ongoing missed opportunity to improve the detection of young patients at risk for premature ischemic heart disease. First, the risk factors that are more common in young adults, such as smoking and low HDL-C, are not independently considered risk enhancers. Young adults with an estimated 5–20% predicted 10-year risk can only receive a class I indication if a risk enhancer is present. Second, neither the 2013 nor 2018 guideline provides comprehensive recommendations for adults younger than 40, who can only become eligible for statin therapy in primary prevention with a class I indication if they have an LDL-C level higher than 190 mg/dl, regardless of their smoking status, body mass index, or other risk factors. The 2018 guideline provides a class IIa recommendation for statins for those aged 20–39 with an LDL-C higher than 160 mg/dL and a risk enhancer, but this recommendation was not enough to target individuals at risk for premature CAD. Finally, while relatively few adults had events before age 40, the development of atherosclerosis precedes clinical events by many years. Adults with a predicted 10-year risk of 20% or more are considered high risk, but very few younger individuals can reach this risk threshold because of the significance of older age in the risk model.

The implementation of risk enhancers on top of the 10-year ASCVD risk score to better identify high-risk young individuals requiring statins is an important step taken by the ACC/AHA 2018 Cholesterol Guideline. Nonetheless, our analysis suggests that the guidelines' ability to identify young adults for statin therapy prior to their first myocardial infarction remains

suboptimal. Several proposed solutions may improve detection of at-risk young adults. First, broader utilization of CAC screening, which is emphasized in the latest guidelines, particularly in younger adults, may lead to detection of those with subclinical atherosclerosis at risk for events. Data from longitudinal cohort studies have shown that CAC can be used to improve risk stratification in young adults. Unfortunately, limited uptake of CAC scoring remains a barrier as CAC scoring is not universally reimbursed, and many are unable to pay the cost out of pocket (212, 213).

Additionally, improvements in screening for risk enhancers is needed to maximize the capture of these risk enhancers. In our study, we did not have access to information on maternal pregnancy complications as they were not collected. Efforts to improve routine capture of these data may improve risk prediction in young women. Alternately, the guidelines may consider upgrading the IIb recommendation to a class IIa recommendation to increase the visibility of the importance of individuals at low or borderline-risk young adults, including treatment of younger adults with 5-7.5% 10-year risk and a risk enhancer and adults with LDL-C between 160 and 190 mg/dL. These two criteria would have identified a further 7.5% of patients for therapy prior to their event, increasing the number of adults identified from 46.4% to 53.9%. Other risk-based methods to identify young adults at risk for MI include recommending statins for those at high lifetime risk (214) or those at high risk compared to age- and sex-matched peers (215). In our cohort, young individuals admitted for a first MI had a higher lifetime ASCVD risk score than the older age categories.

Adults who present with CAD earlier in life are at extremely high risk of recurrent events, highlighting the importance of aggressive secondary prevention (62, 121). In a prospective cohort study of patients with obstructive CAD before age 45, one-third of patients presented with a recurrent cardiovascular or cerebrovascular event within a median time of 5 years. Within a maximum follow-up of 20 years, multiple ischemic recurrences were frequent, despite guideline-

based secondary prevention and premature death occurring in 10% of these young individuals. A similarly high rate of recurrent MI, stroke, or death was observed in the younger individuals in the present study. Nonetheless, in our cohort, fewer than 30% of patients with premature CAD would have been considered very high risk and met criteria for more intensive non-statin lipid-lowering therapy had they failed to achieve an LDL-C level <70 mg/dL on statins alone. While ezetimibe and PCSK9 inhibitors are associated with a significant reduction in major adverse cardiovascular events, including mortality, young individuals are rarely considered eligible, and less frequently deemed eligible than older adults (86,87). Current criteria to be considered very high risk requires the presence of two additional risk factors, which is rare in younger adults. By comparison, being ≥65 years of age is considered a high-risk criteria in and of itself, so the bar for very high risk is essentially lower in older vs. younger adults. In secondary prevention, our data suggest that relatively few younger adults are meeting guideline-based criteria for the most aggressive lipid lowering therapy after their event, despite having a long potential treatment time. Given evidence that the benefit of these therapies increases with time on treatment and provide and absolute reduction in LDL-level, this may be one of the groups to have the most potential benefit on therapy. In contrast with the AHA/ACC guideline, the 2019 European Society task force for management of dyslipidaemia consider all the patients with myocardial infarction as very-high risk and eligible for additional non-statin lipid lowering therapies in case of persistently high LDL-C with statins. Such an approach would increase the overall number eligible for therapy, thereby increasing the cost to the system. As costs have been lowered for PCSK9 inhibitors, and new therapies are made available in the future, cost-related barriers should continue to drop. This approach would also lead to treatment of a population at overall lower risk of recurrent events than just those with risk enhancers, increasing the overall number needed to treat, but would ensure that the benefit of these therapies to the overall burden of disease is maximized.

We demonstrated that very high-risk criteria as presented in the current guidelines do successfully identify individuals at higher risk of fatal events or ischemic recurrences, with a consistent effect across age groups Despite the fact that young adults who were not at very high risk had lower event rates than those considered very high risk, 25 % of them still major adverse ischemic events, suggesting that they could benefit from more aggressive therapy. Statins remain the cornerstone of lipid lowering in secondary prevention, as supported by the recommendation for high intensity statin for all patients <75 years of age with ASCVD in the current and prior guidelines. However, who to treat with additional lipid lowering therapy remains uncertain. Our analysis suggests that the current paradigm of treating only this at highest risk of recurrent events in the short term may lead to large numbers of younger adults failing to meet guideline recommendations for treatment. Analyses from the FOURIER and ODYSSEY trials show no interaction on the relative scale by age (219, 220), and data from long-term follow up of lipid lowering therapy trials shows that the benefit of therapy improves with time on treatment. Thus, those with early onset disease have the highest potential treatment time due to higher overall life expectancy. Given that the recommendation for limiting PCSK9 inhibitors for those at higher risk was largely driven by the cost of therapy, as the price is lowered, the requirement for additional risk factors beyond a single event may be reconsidered.

Study limitations

We acknowledge our study had some limitations. First, patients treated with statins prior to the index event were considered to have class I eligibility for both guidelines. As previously mentioned, not all risk enhancers listed in the 2018 guideline were present in the DDCD (**Online Table 3**). Furthermore, not all risk enhancers are captured in routine clinical practice and were consequently also not part of the Duke Databank dataset, including biomarkers and CAC scoring and history. Familial history of CAD was used as a surrogate for familial history of premature

CAD; similarly, Asian ethnic background was used as a surrogate for South-Asian population because these were not split in the Duke Databank data collection form. By considering any family history of CAD as "premature" and all Asian ethnicity as "South Asian" we may have overestimated the prevalence of this risk enhancer, and potentially over-estimated the number of adults considered at higher risk due to family history. Second, the event rates in our data are likely higher than a contemporary cohort given advances in the treatment of CAD patients. Contemporary cohorts likely have lower absolute event rates; however, this change should not have affected estimates for statin eligibility or the relative difference in event rates by risk status. Because patients may have had MI due to non-atherosclerotic disease (dissection, vasospasm, or type 2 MI), we required both the presence of an MI and obstructive coronary artery disease as an inclusion criterion in the cohort. Thus, our findings should only be extrapolated to adults with angiographically proven obstructive coronary artery disease. In addition, we attempted to identify a cohort of patients with newly diagnosed ASCVD presenting with myocardial infarction and obstructive coronary artery disease. However, we were unable to determine whether patient had previously been diagnosed with nonobstructive CAD, as this was not captured in the Duke Databank. Thus, our sample may have included some patients with previously diagnosed disease. Those who were taking statins for that indication would have been considered "eligible" in our analysis.

CONCLUSIONS

The majority of adults with premature CAD would not have been recommended for statin therapy prior to their first MI according to criteria from both the 2013 and 2018 ACC/AHA guidelines. Younger individuals are also less frequently eligible for secondary prevention with intensive non-statin lipid-lowering therapies compared with older adults, despite having a much longer potential lifespan for recurrent events. Young individuals with very high-risk criteria are at higher risk of major adverse cardiovascular events, supporting the appropriate implementation of intensive lipid-lowering therapies in these patients.

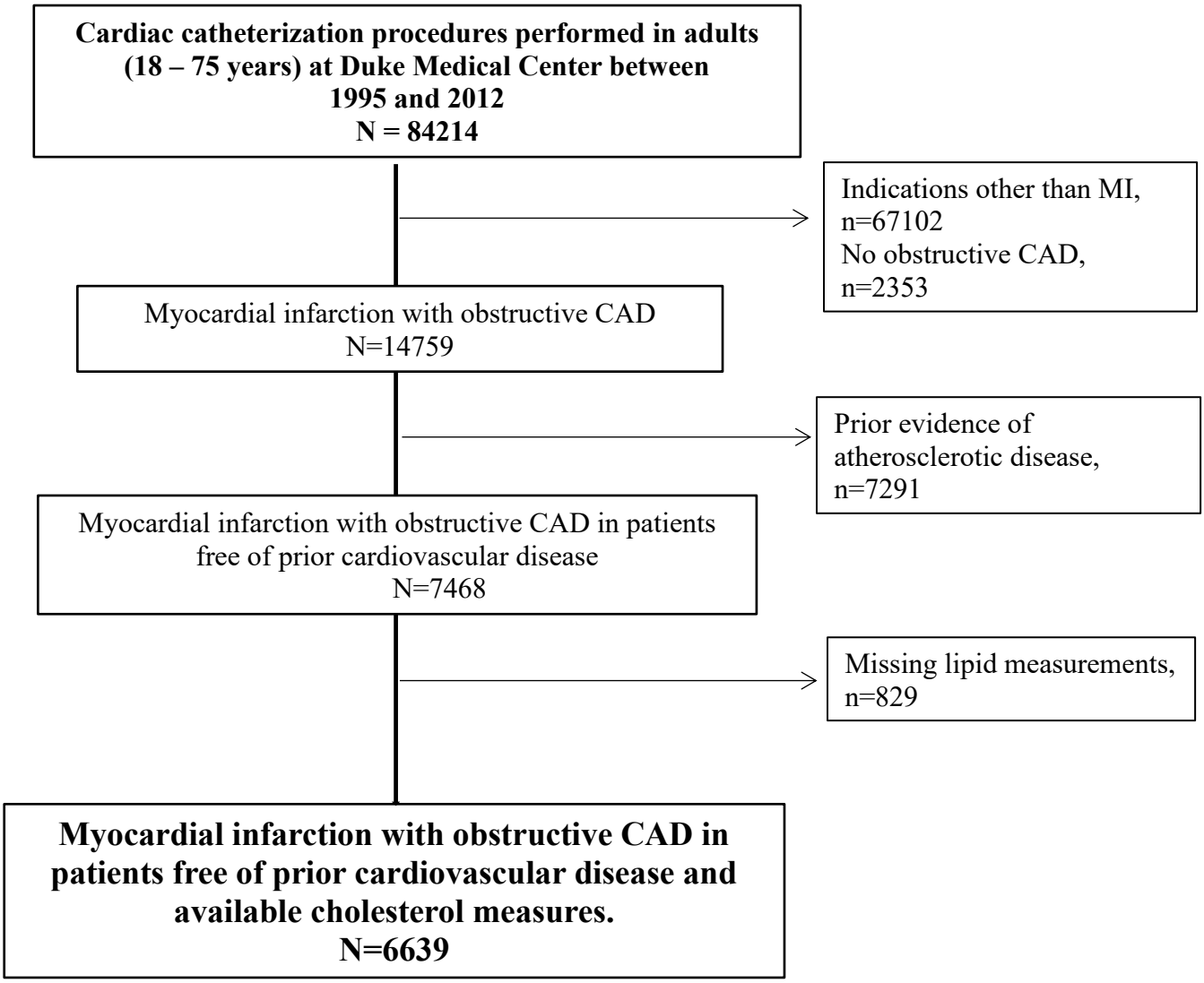
PERSPECTIVES

Competency in medical knowledge: Despite the inclusion of specific risk enhancers, one out of two patients admitted for a premature MI would not have met the guideline criteria for statins in primary prevention. Younger patients were also less likely to have very high-risk criteria for intensive lipid-lowering therapy, despite a high rate of subsequent major cardiac events.

Translational outlook: Better implementation of risk enhancers with a specific approach to recognize and treat ASCVD is needed to improve the primary and secondary outcomes of young patients.

SUPPLEMENTAL MATERIAL

Online Figure 1. Selection of Patients for Inclusion in Study Cohort



Online Table 1. Criteria for Eligibility for Statins in Primary Prevention According to 2013 and 2018 ACC/AHA Cholesterol Guideline

2013 ACC/AHA Blood Cholesterol Guideline		2018 ACC/AHA Blood Cholesterol Guideline	
Age >18 years		**Age >18 years**	
LDL-C ≥190 mg/dL	Class I	LDL-C ≥190 mg/dL	Class I
In adults 40-75 years with LDL-C between 70-189 mg/dL		**In adults 40–75 years with LDL-C between 70-189 mg/dL**	
Diabetes	Class I	Diabetes	Class I
10-year ASCVD risk ≥7.5%	Class I	10-year ASCVD ≥20%	Class I
10-year ASCVD risk ≥5-7.5%	Class IIa	10-year ASCVD >7.5-<20% + risk enhancer	Class I
-		10-year ASCVD >7.5-<20 %	Class IIa
		In adults 20-39 years	
		LDL-C ≥160 + risk enhancer	Class IIa

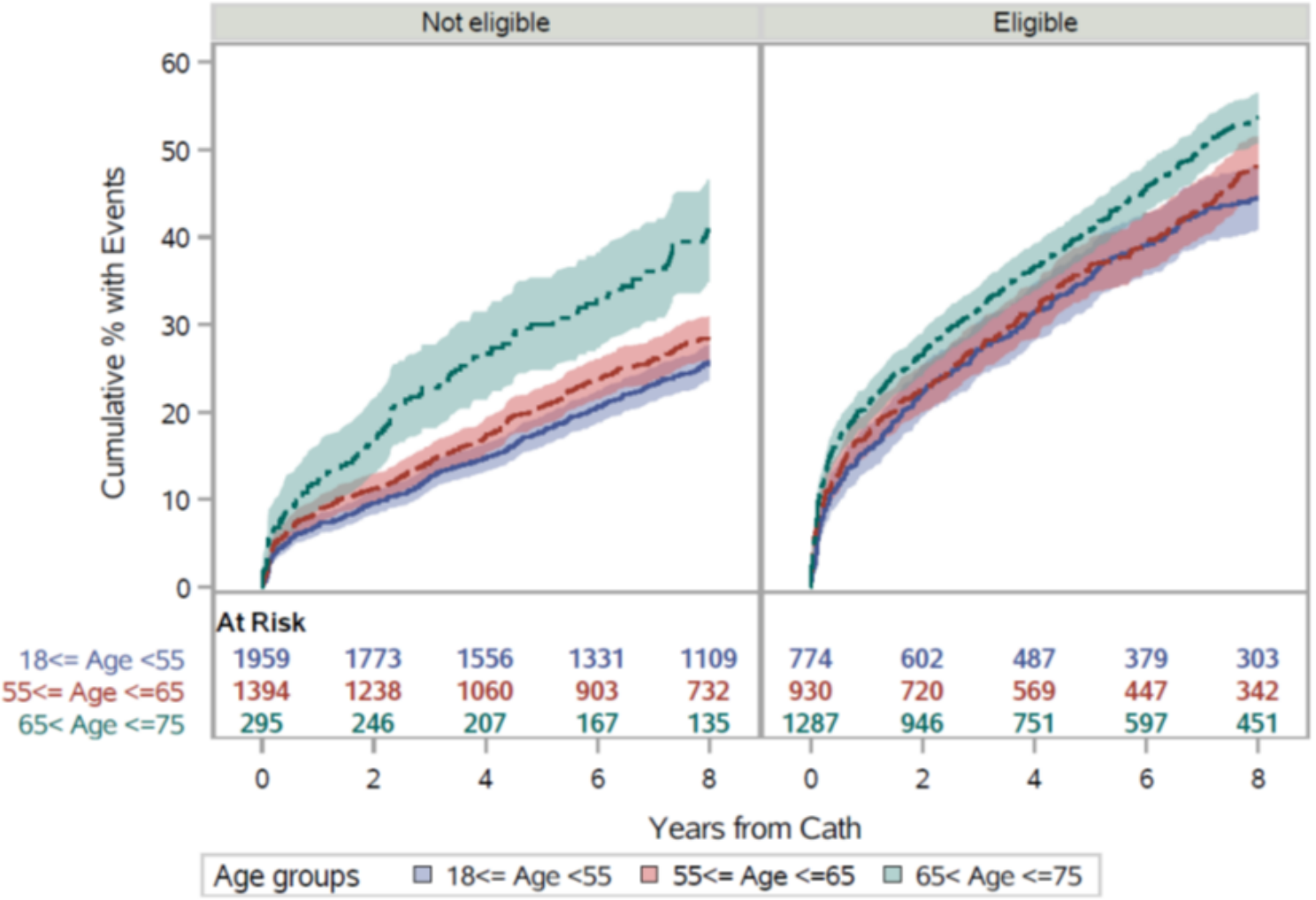
ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol

Online Table 2. Available Risk Enhancers and Surrogates in DDCD

	Risk Enhancers in 2018 ACC/AHH Guideline	Risk Enhancers Available or Surrogated in the DDCD
Clinical	Familial history of premature ASCVD	Familial history of CAD
	eGFR <60 mL/min/1.73 m²	eGFR < 60 mL/min/1.73 m²
	Metabolic syndrome	Metabolic syndrome was defined as the presence of at least three of the following criteria: BMI ≥30Kg/m, baseline triglycerides ≥175 mg/dL, baseline HDL-C <40 mg/dL for men and <50 mg/dL for women, hypertension or anti-hypertensive drug, and diabetes.
	Inflammatory diseases	HIV, connective tissue disease
	South Asian	Asian
Conditions specific to women	Premature menopause (before 40 years-old)	Premature menopause (before 40 years-old)
	Pregnancy-associated disorders (preeclampsia, hypertension, gestational diabetes)	None
Biology	Persistently elevated LDL-C ≥160 mg/dL	Unavailable
	Persistently elevated triglycerides ≥175 mg/dL	Baseline triglycerides ≥175 mg/dL
	hs-CRP ≥2.0 mg/L	Unavailable
	Lp(a) levels >50 mg/dL or >125 nmol/L	Unavailable
	apoB ≥130 mg/dL	Unavailable
	CAC score	Unavailable

ACC = American College of Cardiology; AHA = American Heart Association; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; CAD = coronary artery disease; DDCD = Duke Databank for Cardiovascular Disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity c-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein a

Online Figure 2. Cumulative Incidence of Death, MI, or Stroke, Stratifier by Whether Patients Met Eligibility Criteria for Intensive Lipid-lowering Therapy, and by Age Groups



7.2019 ESC/EAS Guidelines for management of dyslipidaemia: strengths and limitations

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CONDENSED ABSTRACT

In 2019, the European Society of Cardiology and European Atherosclerosis Society released a new guideline document with substantial changes regarding the assessment of cardiovascular risk and treatments. The update of high-risk criteria and categories led to a better detection and primary prevention of patients at risk of a first cardiovascular event. Nonetheless, additional efforts are needed for a better inclusion of risk modifiers, especially specific to women, to improve risk stratification and direct primary prevention. Eventually, we discuss how these new guidelines implement PCSK9 inhibitors for very-high risk individuals and the evidence supporting new LDL-C goals below such as 55 mg/dL and 40 mg/dL.

ABBREVIATIONS

ESC European Society of Cardiology

EAS European Atherosclerosis Society

PCSK9 Proprotein convertase subtilisin/kexin type 9

LDL-C Low density Lipoprotein Cholesterol

SCORE Systematic Coronary Risk evaluation

ASCVD Atherosclerotic cardiovascular disease

AHA American Heart Association

ACC American College of Cardiology

INTRODUCTION

Three years after the 2016 Guidelines for the management of dyslipidemia and Cardiovascular prevention, the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) released a new guideline document with substantial changes regarding the assessment of cardiovascular risk and treatments (57, 221, 222). Following the important evidence brought by trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, the *2019 ESC/EAS Guidelines for the management of dyslipidemias* reshaped the therapeutic algorithms and Low density Lipoprotein Cholesterol (LDL-C) goals (71, 133, 223).

The 2019 ESC/EAS task force also renewed the Systematic Coronary Risk evaluation (SCORE) as a pivotal model to stratify the cardiovascular risk and guide the decision of statins and intensive lipid lowering therapies for primary prevention (126). An additional step towards a tailored prevention is taken with the consideration of risk modifiers, measurement of non-LDL-C lipid metabolite targets and imaging techniques to better stratify the individual risk. A recent population-based study has demonstrated that the implementation of new LDL-C goals and consideration of elderly as eligible for primary prevention have improved the performance of the guidelines to detect individuals at risk of a first myocardial infarction (224).

This review sought to describe how the novel 2019 *ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk* changed cardiovascular prevention strategies, implemented new lipid-lowering therapies and their clinical impact on daily practice.

SCORE(s) and its limitations in Europe

Systematic Coronary Risk evaluation (SCORE)

The SCORE model remains the cornerstone to evaluate the risk of cardiovascular death in the 2019 ESC/EAS Dyslipidemia Guidelines. The SCORE model – first introduced in the 2003 ESC guideline - predicts the risk of a fatal cardiovascular event at 10 years in apparently healthy individuals (225). The SCORE model was derived from 12 European cohort studies assembling 3-million person-years of observation and nearly 8000 fatal cardiovascular events identified with the International Classification of Diseases (226). Countries are categorized as low-risk if their age-adjusted 2016 cardiovascular mortality rate was below 150 per 100 000 inhabitants, and high-risk for countries with a higher rate of cardiovascular death **(table 1).**

Table 1. Risk estimation in the SCORE model for European and Mediterranean countries.

Countries with a low CV risk Cardiovascular death rate < 150 per 100 000 habitants	**Countries with a high CV risk Cardiovascular death rate ≥ 150 per 100 000 habitants**
Austria	Albania
Belgium	Algeria
Cyprus	Armenia
Denmark	Bosnia and Herzegovinian
Cyprus	Croatia
France	Czech Republic
Germany	Estonia
Greece	Hungary
Iceland	Latvia
Ireland	Lebanon
Israel	Libya
Italy	Lithuania
Luxembourg	Montenegro
Netherlands	Morocco
Norway	Poland
Malta	Romania
Portugal	Serbia
Slovenia	Slovakia
Spain	Tunisia
Sweden	Turkey
Switzerland	
United Kingdom	

The three important aspects of the SCORE model are the followings:

1. There are two different models for low-risk and high-risk regions, based on their cardiovascular mortality estimated by the World Health Organization **(table 1).**
2. The SCORE model is used to assess the risk of cardiovascular death in apparently healthy individuals, but is not to be used in individuals with prior ASCVD, type 1 or type 2 diabetes, chronic kidney disease, as they are considered at very-high risk and need active management of all risk factors.
3. The most important variables in the SCORE model are sex, age, and smoking status along with blood pressure and total cholesterol

Current limitations of the SCORE model

. The SCORE model relies on the analysis of observational cohorts and death certificates collected between 1967 and 1991, with a question mark regarding their applicability to the contemporary European population (227, 228).Data from population-based studies and prospective longitudinal cohorts of healthy individuals are needed to develop models aiming to predict the risk of a first cardiovascular event (rather than just cardiovascular death) and direct appropriate primary prevention intervention and therapies. In addition, the SCORE model is not applicable to individuals below the age of 40 years, age at which primary prevention could play an important role to prevent premature cardiovascular events in the 10 subsequent years.

Risk modifiers: time for action

Risk modifiers (ESC) versus Risk enhancers (AHA/ACC)

Following the ACC/AHA 2018 Cholesterol guidelines that implemented a list of "risk enhancers" in the decision-algorithm to stratify risk and assign primary prevention statins, the 2019 ESC/EAS Task Force provided a list of "risk modifiers" **(table 2).** Many of these factors have a well-established association with atherosclerotic burden such as chronic inflammatory

disease, HIV or chronic kidney disease (229, 230). Importantly obesity and metabolic syndrome are included as risk modifiers, considering their association with increased cardiovascular morbidity and mortality even in the absence of traditional risk factors (231, 232). Although the range of therapeutic intervention is limited, the implementation of social deprivation and psychosocial stress as a risk marker is also an improvement towards a tailored approach of the cardiovascular risk (233). Other factors made are in the list, such as left ventricular hypertrophy and atrial fibrillation.

While this constitutes a progress in the acknowledgment of the contribution of non-traditional cardiovascular factors to the development and prognosis of atherosclerosis, several limitations are to be noted. A more straightforward implementation of these risk modifiers in the decision algorithms to initiate lipid lowering therapy in individuals at low or intermediate risk could improve the performance of the guidelines to detect individuals at risk and direct primary prevention. (229). Secondly, risk enhancers specific to women – such as early menopause, gestational hypertension or diabetes- are not considered (234, 235). This failure to provide sex-specific risk modifiers is an important gap in the present guideline, as cardiovascular disease has become the first cause of death in women, and the rate of young women admitted for acute myocardial infarction has doubled in the past 15 (64, 236). Similarly, the absence of ethnic-specific risk modifiers is another gap that needs to be filled to provide a tailored approach for high risk subgroups vulnerable to premature coronary artery disease (121).

Biologic and imaging risk modifiers

The 2019 ESC/EAS Task Force proposes Apolipoprotein B and Lipoprotein(a) as biological risk modifiers. Strong evidence supports the association of Apolipoprotein B with the risk of fatal myocardial infarction in both men and women, and across age groups (137). Similarly, large cohort studies have demonstrated an association of Lp(a) with the risk of

coronary heart disease and stroke – although its added value on top of LDL-C and HDL-C measures is modest (237) (238). In the ESC/EAS 2019 Dyslipidemia guidelines, patients with a Lp(a) level above 180 mg/dL are considered at high risk – which complements the ACC/AHA and EAS recommendation for a target Lp(a) below 50 mg/dL (239). Nonetheless, it is unclear how these factors should be used in the decision to initiate treatment, and how much they should weigh with other risk factors.

CAC score and plaques on arteries

On top of clinical and biologic risk modifiers, the 2019 ESC/EAS task force included CAC score and plaque on carotid or femoral arteries as risk modifiers and potential triggers for therapeutic intervention. Most of the evidence supporting the use of CAC score is derived from longitudinal cohort studies that demonstrated a strong correlation between the presence of coronary calcium and CAD (240, 241). There are considerable data supporting that CAC score improves cardiovascular risk reclassification, especially with a good negative predictive value (242).

Table 2. List of risk modifiers provided by ESC and risk enhancers provided by ACC/AHA

	Risk modifiers in 2019 ESC Guideline	Risk enhancers in 2018 ACC/AHH Guideline
Clinical	Familial history of premature cardiovascular disease	Familial history of premature ASCVD
	Chronic kidney disease	Chronic kidney disease
	Obesity	Metabolic Syndrome
	Chronic immune-mediated inflammatory disorder	Inflammatory diseases
		Ethnicity
		Conditions specific to women: pre-eclampsia, premature menopause
	Psychosocial stress	
	Physical inactivity	
	Major psychiatric disorders	
	Treatment for HIV	
	Atrial fibrillation	
	Left ventricular hypertrophy	
	Social deprivation	
	Obstructive sleep apnea	
	Non-alcoholic fatty liver disease	
Biology		Persistently elevated LDL-C ≥ 160 mg/dL
	HDL-C	HDL-C
		Persistently elevated triglycerides ≥ 175 mg/dL
		hs-CRP ≥ 2.0 mg/L
	Lp(a) > 180 mg/dL or > 430 nmol/L	Lp(a) levels > 50 mg/dL or > 125 nmol/L
	Apoliprotein B	apoB ≥ 130 mg/dL
Imaging	Arterial plaque burden (carotid or femoral)	
	CAC score assessment	CAC score

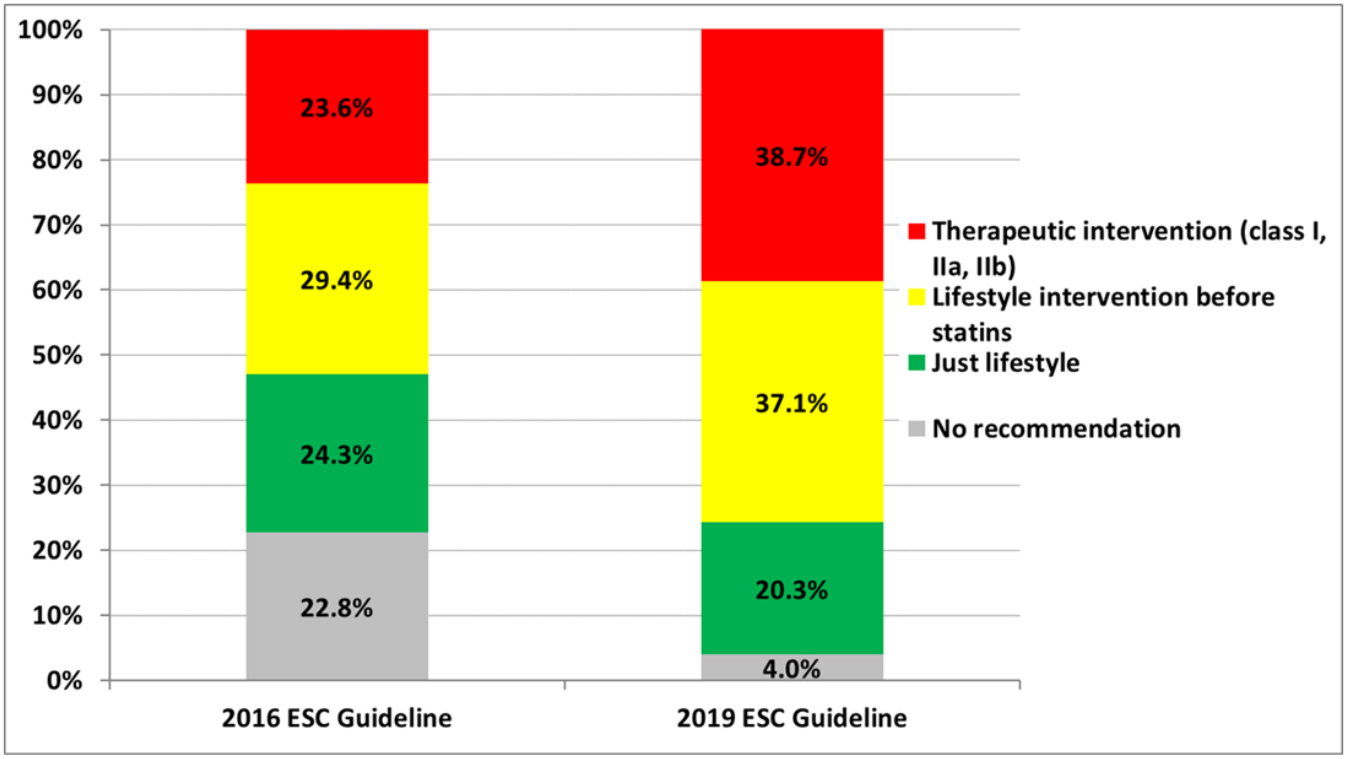
Is the new guideline efficient to trigger decisions in primary prevention?

According to LDL-C levels

The 2019 ESC guideline of cholesterol broadened modestly the range of patients eligible for a therapeutic intervention in the setting of primary prevention. The only notable change concerns patients with a baseline LDL-C above 190 mg/dL who are now eligible for statins on top of lifestyle intervention. Such high thresholds before qualifying for statin therapy is in contrast with 2018 ACC/AHA Cholesterol guideline – in which intermediate or borderline risk patients would be eligible in the presence of risk enhancers or if LDL-C is above 160 mg/dL. The 2019 ESC/EAS Dyslipidemia guidelines fail to broaden therapy to these moderate risk individuals, despite the strong evidence of benefits in this category – with a 15 % reduction of mortality for each reduction of 30 mg/dL in LDL-C levels (214).

When using clinical and biological data of the prospective French ePARIS registry (178), 23.6 % of patients admitted for a first STEMI would have met the criteria of ESC/EAS 2016 Dyslipidemia Guidelines to be treated with a statin prior to their event the 2016 ESC/EAS Guidelines . The 2019 ESC/EAS Guidelines improved the detection to 40 % of the individuals eligible for primary prevention statins prior to a first STEMI **(figure 1).**

Figure 1. Performance of the 2019 ESC Guideline to detect and treat individuals with statins before they develop a first myocardial infarction (data from 2757 individuals of e-PARIS registry)



Several factors explain the failure to provide primary prevention in patients who will further develop an acute myocardial infarction. The first is the pivotal importance of the SCORE system, aiming to describe the risk of cardiovascular death at 10 years, and not the risk of cardiovascular events; as a result, non-fatal myocardial infarction, unstable angina and stroke are not taken into account in the algorithm, underestimating the need for statins in the overall population. Secondly, although a new target of 55 mg/dL LDL-C was introduced for secondary prevention, there was no change in the LDL-C target in primary prevention for high-risk patients, a target which is still 70 mg/dL.

Performance of primary prevention according to age

The 2019 ESC/EAS guideline fails to detect 4 out 5 patients aged 55 years or less who developed a first myocardial infarction in the ePARIS cohort. This is an important gap, as population-based surveys have demonstrated increasing rates of young patients admitted for acute myocardial infarction. In a Danish cohort study describing the rate of admissions for myocardial infarction between 1978 and 2012 by age and sex, there was an increase of 26 % and 95 % in the rate of men and women admitted before the age of 50 years. In all the other age categories, the rate of myocardial infarction decreased (243).

In contrast, the SCORE risk board has been extended to patients aged 70 years or above, and a class I recommendation has been issued for therapeutic intervention between 70 and 75 years of age according to the risk category. Furthermore, the 2019 ESC task group provided a class IIb recommendation with a level B of evidence for the treatment of high risk and very high-risk patients aged 75 years or more. This recommendation is in line with the recent metanalysis of the Cholesterol Treatment Trialists demonstrating only a modest effect of statins in primary prevention of patients aged 75 years or more with no adverse effects on cancer or non-cardiovascular mortality (244).

Performance of primary prevention according to sex

Scores aiming at evaluating cardiovascular risk have been well described as less efficient in women than men (141, 245). Nonetheless, latest 2019 ESC/EAS Dyslipidemia guidelines improved the detection of women at risk of a first myocardial infarction in the ePARIS registry – with a two-fold increase in their eligibility for primary prevention with statins. This is of importance, considering the large amount of evidence regarding the safety and benefits of statins regardless of sex(215). This improvement in the detection of women at risk occurs despite the

absence of implementation of sex-specific risk modifiers and is mostly driven by the extension of recommendations for therapeutic intervention to older individuals.

Treatment initiation with statins

The 2019 ESC/EAS Dyslipidemia Guidelines recommend the direct measure of LDL-C over the use of the Friedwald formula, as it is more reliable especially in case of elevated triglycerides (246). Statins should be initiated with the highest tolerated dose to reach the LDL-C goal determined by the individual's risk category – rather than selecting the dose according to baseline LDL-C guideline as recommended by ACC/AHA guideline. This "treat to target" strategy – as opposed to "treat and forget" - is supported by a large range of evidence, starting with the meta-analysis Cholesterol Treatment Trialists, demonstrating that each reduction of 30 mg/dL in LDL-C levels reduces the risk of major ischemic events by 40 to 50 % (247), (248), (249).

Primary prevention with intensive lipid-lowering therapies

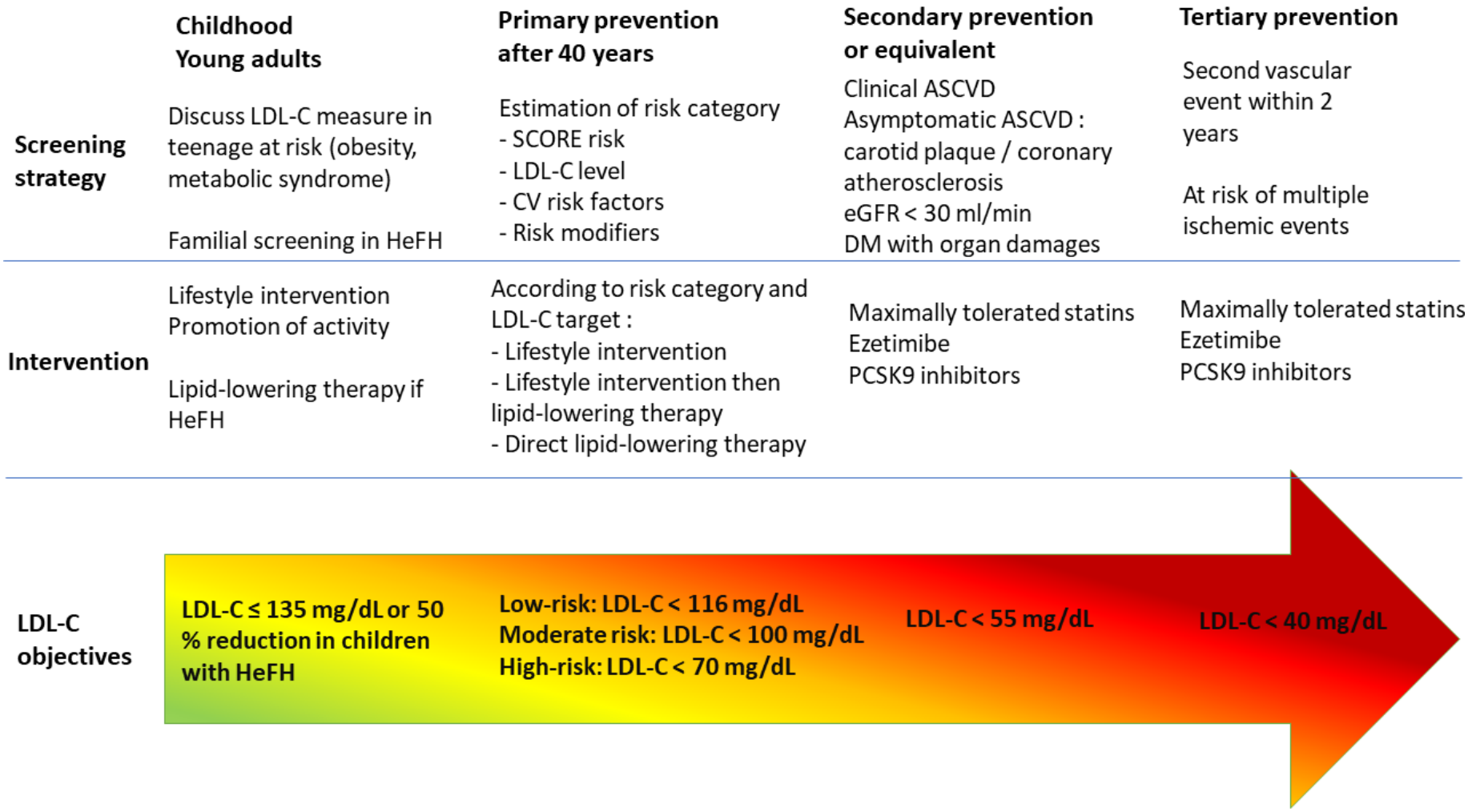
The ESC/EAS 2019 Dyslipidemia guidelines open the door to intensification of primary prevention with PCSK9 inhibitors in very-high risk patients (risk SCORE > 10 %, chronic kidney diabetes, diabetes with 3 other risk factors) with uncontrolled LDL-C under statin and ezetimibe, with a class IIb, level of evidence C. Such recommendation relies on an extrapolation of the evidence provided by clinical trials of PCSK9 inhibitors and ezetimibe, as FOURIER and ODYSSEY trials only included individuals with a symptomatic ASCVD or a recent acute coronary syndrome. There are abundant data supporting the concept of "the lower LDL-C, the better" in the primary prevention of patients at risk of cardiovascular disease (250, 251). Eventually, the ongoing VESALIUS-CV trial (NCT03872401) is currently evaluating the effects of Evolocumab in the primary prevention of patients at high cardiovascular risk.

Secondary prevention: novel therapies, novel targets

Very-high-risk category

The 2019 ESC/EAS Dyslipidemia Guidelines have provided an important upgrade regarding the spectrum of secondary prevention, by including asymptomatic patients with established atherosclerosis on imaging exams – such as carotid plaques on ultrasound or coronary atherosclerosis on coronary angiography CT scan – in the "very high-risk" category **(figure 2**). Very-high-risk individuals now also include patients with diabetes and organ damage, chronic kidney disease and SCORE risk superior to 10 %.

Figure 2. Screening and intervention strategies with LDL-C objectives according to 2019 ESC/EAS Dyslipidaemia guidelines.

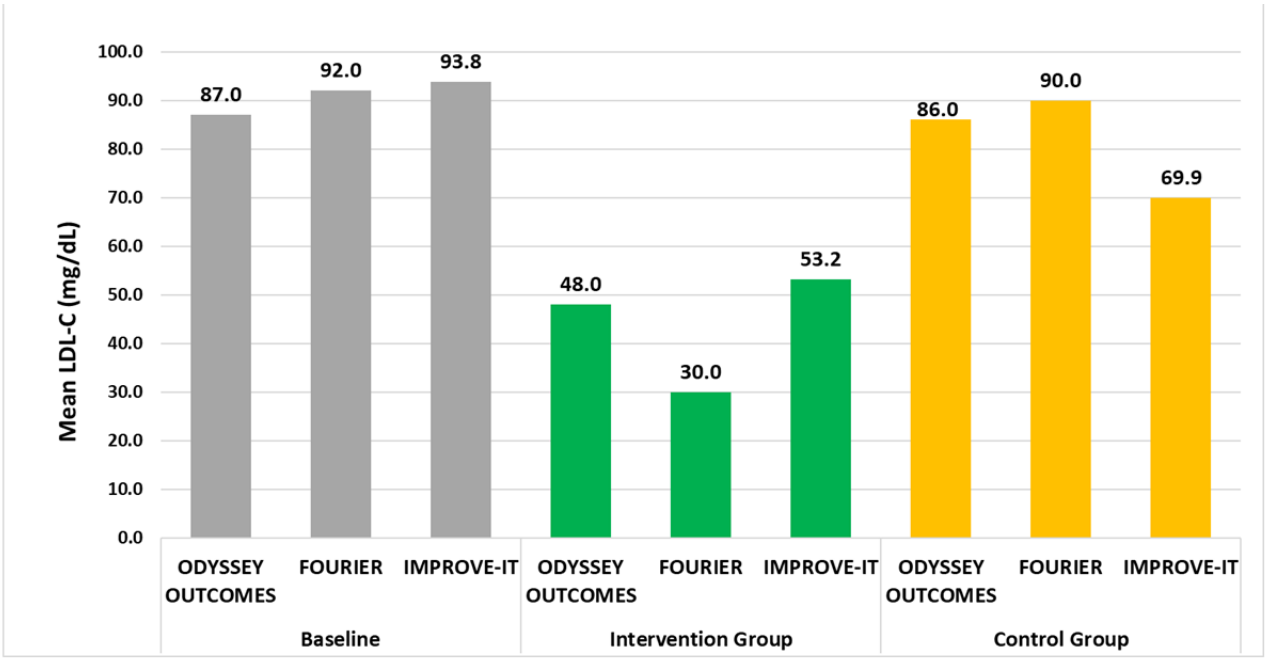


Ezetimibe on top of statins

The 2019 ESC/EAS Dyslipidemia Guidelines upgraded the recommendation to add ezetimibe on top of the maximal tolerated dose of statins in individuals not meeting the LDL-C goal related to their risk categories from a class IIa to a class I category.

Ezetimibe uses a different path than statins by selectively inhibit intestinal cholesterol absorption (252). The landmark clinical evidence supporting the combination of ezetimibe and statins came from the IMPROVE-IT trial (216) which included 18,144 with a recent acute coronary syndrome (10 days) and LDL-C above 50 mg/dL. Ezetimibe on top simvastatin was associated with a reduction in major outcomes (composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization or nonfatal stroke) versus a well-treated group by statins alone (mean LDL-C 69.9 mg/Dl), and thus reinforced the concept of « lower LDL-C is better » **(figure 3).**

Figure 3. Effect of intensive lipid lowering therapies on LDL-C levels in trials of intensive lipid-lowering therapies



PCSK9 inhibitors on top of statins and ezetimibe in very-high-risk patients

Following the evidence brought by the FOURIER (Evolocumab) and ODYSSEY (Alirocumab) outcome trials, the ESC/EAS 2019 Dyslipidemia Guidelines has recommended the use of PCSK9 inhibitors for the secondary prevention of very-high risk individuals not at LDL-C goal LDL-C (> 55 mg/dL) despite maximally tolerated statin doses and ezetimibe, with a class I recommendation and a level B of evidence **(figure 3 and table 3)** (71, 133).

Both trials resulted in reductions in LDL-C levels by 60 % from baseline and a consistent 15 % reduction in the risk of major adverse cardiovascular and cerebrovascular events. This was associated with reassuring safety data regarding both the drugs used and the extreme reduction in LDL-C levels (223), (220, 253).

Table 3. Characteristics of Evolocumab and Alirocumab

	Evolocumab	**Alirocumab**
Type of molecule	Monoclonal Antibody	Monoclonal Antibody
Trial	FOURIER	ODYSSEY outcome
Number of patients included	27 564 individuals with LDL-C ≥ 70 mg/Dl and either: - history of myocardial infarction - Ischemic stroke - symptomatic peripheral artery disease	18 924 individuals with an acute coronary syndrome 1 to 12 months before randomization and LDL-C ≥ 70 mg/dL
Posology	Regimes of 140 mg every 2 weeks or 420 mg every 4 weeks	150 mg subcutaneous every 2 weeks
Pharmacokinetics	Maximum suppression within 4 hours of administration T max 3 - 4 days Estimated bio availability 72 % T 1/2 11 - 17 days	Maximum suppression within 4 to 8 hours of administration T max 3 - 7 days Estimated bio availability 85 % T 1/ 17 to 20 days
Primary endpoint	cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	Death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.
Results	Intervention: 9.8% Control: 11.3% HR = 0.85; 95% CI 0.79 to 0.92 ; P<0.001 Number needed to treat= 63	Intervention: (9.5%) Control: 11.1%) HR = 0.85; 95% CI, 0.78 to 0.93; P<0.001 Number needed to treat=63

LDL-C thresholds: is the lower the better?

Going a step beyond the evidence in the current literature, the 2019 ESC/EAS Dyslipidemia Guidelines have recommended an LDL-C target of 55 mg/dL in all individuals with very-high-risk criteria. When maximal dose statins and ezetimibe fail to reduce LDL-C levels below 55 mg/dL, the introduction of PCSK9 inhibitors is recommended (class I A, level of evidence A). This threshold is even lowered to 40 mg/dL in patients with a recurrent ischemic event within 2 years of a myocardial infarction (class IIB, level of evidence B) **(figure 2**). The prior 2016 ESC/EAS Dyslipidemia guidelines recommended an LDL-C target below 70 mg/dL in the setting of secondary prevention. The same LDL-C target below 70 mg/dL was recommended in 2018 by the ACC/AHA Cholesterol Guidelines before considering the addition of PCSK9 inhibitors in very high-risk patients. Interestingly, FOURIER and ODYSSEY OUTCOMES trials included patients with a baseline LDL-C above 70 mg/dL under maximal tolerated statins dose

Nonetheless, the use of a target LDL-C of 55 mg/dL rather than 70 mg/dL is crucial to implement PCSK9 inhibitors and gain their benefits to further reduce cardiovascular events, including mortality (72) :

1. An LDL-C threshold of 55 mg/dL opens the window for intensification with PCSK9 inhibitors in a reasonable half of individuals already on statins and ezetimibe **(Figure 3)** (216).
2. Earlier is better. In the Treat Stroke to Target trial, it took nearly 1 year to decrease the LDL-C below 70 mg/dL despite 99 % of patients treated with moderate to high intensity statins and 25 % of combination ezetimibe. An earlier initiation and a better implementation of PCSK9 inhibitors is associated with a reduction the risk of recurrent ischemic (254).

3. Lower LDL-C is better (214, 247–249). The important benefits of PCSK9 inhibitors on ischemic events, including mortality in ODYSSEY OUTCOMES trial, cannot be separated from the LDL-C levels observed at one 1 year, measured between 30 and 40 mg/Ll.
4. Lower LDL-C is safe. There were no reports of adverse events related to the extreme reduction of LDL-C levels in the landmark trials and meta-analysis of data regarding PCSK9 inhibitors (223). Long-term follow-up should provide additional data on the safety of PCSK9 inhibitors.

Challenges, novel targets and unmet needs

Screening strategies	Primary prevention	Secondary prevention	Tertiary prevention
Update of the SCORE	Improve lifestyle	Early use of PCSK9 inhibitors in very-high-risk categories	Early use of novel lipid-lowering therapies in individuals at risk of multiple events (premature CAD, chronic inflammation)
Inclusion of non-fatal cardiovascular events in the risk stratification	Smoking cessation	Inclirisan for a sustained PCSK9 inhibition (ORION-11)	Specific LDL-C level targets
Inclusion of risk modifiers in decision algorithms	Compliance to statins	CSL112 to improve Cholesterol Efflux Capacity and HDL-C function (AEGIS II)	Multimodal cholesterol assessment and biological thresholds
Inclusion of sex-specific risk modifiers	Multimodal cholesterol assessment in populations at risk : - Lipoprotein a - Cholesterol efflux capacity - apolipoprotein B	Icosapent ethyl in high risk individuals with elevated TG despite statins	Multimodal cholesterol therapies.
Inclusion of ethnic-specific risk modifiers	PCSK9 inhibitors in very-high-risk categories with uncontrolled LDL-C.		Combination of aggressive lipid-lowering therapies and treatments targeting residual risk
Provide age-specific strategies (premature CAD)	Icosapent ethyl in high risk individuals with elevated TG despite statins		

Implementing PCSK9 inhibitors

The 2019 ESC/EAS Dyslipidemia Guideline used a pragmatic and efficient LDL-target threshold to implement the use of PCSK9 inhibitors for very-high risk patients. Of importance, FOURIER and ODYSSEY outcomes evaluated the effect PCSK9 inhibitors introduced within the year of MI. There are important reasons to suggest that the early use of PCSK9 inhibitors could provide additional benefits shortly after myocardial infarction when PCSK9 levels are very high and when statins have been shown to be effective (254).

Sustained PCSK9 inhibition with small interfering RNA

The ORION-1, 10 and 11 studies study demonstrated that Inclirisan – a small interfering RNA that inhibits the intracellular hepatic translation of PCSK9 – provided a sustained LDL-C reduction (from 30 to 40 % at 1 year) with one or two doses a year (255) (256). A phase III trial is currently evaluating the clinical efficacy of inclisiran on MACE in ASCVD patients (Orion 4, NCT NCT03705234).

HDL-C, apolipoprotein A-1 and Cholesterol efflux capacity as therapeutic targets

The cholesterol efflux capacity – largely mediated by HDL-C - from arterial tissues to liver via macrophages has demonstrated its association with major adverse cardiovascular events (178, 257, 258). While CETP inhibitors significantly increased HDL-C levels in trials, they have not displayed benefits on cardiovascular outcomes (259–261).

The possibility to improve cardiovascular outcomes by improving HDL-C function (rather than by increasing HDL-C levels and cholesterol efflux capacity is currently being explored with CSL112 infusions (plasma derived apolipoprotein A-1)(262). Four infusions of CSL112 were associated with increased apoA-I levels and improved cholesterol efflux in the

AEGIS I trial (Apo-I Event Reducing in Ischemic Syndromes)(263). Following these observations, the AEGIS II trial (NCT03473223) is currently evaluating CSL112 infusions to reduce major adverse cardiovascular events in patients admitted for acute coronary syndromes.

Targeting Hypertriglyceridemia

Hypertriglyceridemia is a well-described contributor to the residual cardiovascular risk (264). The recent REDUCE-IT trial have demonstrated that icosapent ethyl on top of statins was associated with a 25 % relative risk reduction and a 4.8 % absolute risk reduction in the risk of major adverse cardiovascular events in high-risk diabetics or individuals with established cardiovascular disease (265). The 2019 ESC/EAS Dyslipidemia Guidelines implemented the use of icosapent ethyl 2 g twice daily in high risk individuals with persistently triglyceride levels between 1.5 and 5.6 mmol/L (135 and 499 mg/dL) under statins. Research on antisense oligonucleotide against apolipoprotein-CIII mRNA is another promising path for individuals with hypertriglycemia (266).

Improving adherence

Lipid-lowering treatments only work in individuals who take them. This has been a particular challenge as negative statin-related stories in the media have contributed to poor compliance with a subsequent increase in cardiovascular mortality according to nationwide cohort studies (267, 268). Findings from the EUROASPIRE IV survey has demonstrated that patients with cardiovascular disease were frequently inadequately treated and outside of LDL-C targets (269). This highlights the need for active reassurance and information, as well as efforts to “treat to target” with regular monitoring of LDL-C levels. Providing the appropriate dose with moderate or high intensity statins for high-risk patients is paramount to reduce cardiovascular

events – even when LDL-C goals are achieved (270). Future guidelines will have to provide strategies aiming at improving adherence to lipid-lowering therapies and lifestyle interventions.

CONCLUSIONS

The 2019 ESC/EAS Dyslipidaemia guidelines have reshaped the face of prevention with several important upgrades by 1/ considering patients with asymptomatic atherosclerosis or organ damage as very-high-risk patients requiring drug intervention 2/ recommending an active follow-up of LDL-C targets with an escalated algorithm therapeutic approach 3/ providing profound and sustained LDL-C reduction using PCSK9 inhibitors to further improve cardiovascular outcomes in secondary prevention, as well as tertiary prevention in individuals with multi-ischemic recurrences. The future ESC/EAS task force will have to focus on a better risk stratification in primary prevention, be more inclusive of sex-specific risk modifiers and implement the evidence of the many ongoing therapeutic trials of novel lipid-lowering therapies. 4/ By using a common risk stratification scale as for diabetes or chronic coronary syndrome leading to consistent recommendations.

VI. DISCUSSION ET PERSPECTIVES

1. Importance de l'hérédité coronaire : discussion sur la prédisposition génétique

Les **études 1 et 2**, respectivement française et américaine, ont permis de mettre en évidence le phénotype de patients atteints d'athérosclérose coronaire prématurée ainsi que différents modes d'entrée dans la maladie. La comparaison des deux registres met en avant des points communs mais également des divergences importantes dans les profils observés. Parmi les points communs, on note en premier lieu la présence d'une hérédité coronaire importante dans les deux registres – présente à 40 % - contre 15 à 20 % chez les patients admis pour une maladie coronaire à un âge classique. Cette dimension importante de l'hérédité familiale semble être le reflet direct de la contribution de potentiels polymorphismes génétiques dans la vulnérabilité à développer une athérosclérose précoce, mais également de la transmission et de la reproduction familiale de l'environnement, des facteurs de risque, des habitus et du niveau socio-économique.

Dans **l'étude 2**, le taux d'hypercholestérolémie familiale génétiquement prouvée était de 1%, ce qui est inférieur à ce qui est décrit dans la littérature. On observait 5% d'individus ayant un LDL-C initial supérieur à 190 mg/dl, habituellement associé à la présence de polymorphisme génétique freinant la clairance du LDL-C ; cette proportion d'individus ayant un LDL-C supérieur à 190 mg/dl était surtout élevée (11%) chez les patients présentant de l'athérosclérose coronaire obstructive avant 35 ans. Ainsi, les mutations du LDL-C récepteur, de l'apolipoprotéine B ou du gène de PCSK9 restent des explications marginales et insuffisantes pour expliquer l'ensemble de la contribution génétique aux niveaux élevés de cholestérol et au développement de l'athérosclérose prématurée, et a orienté les chercheurs vers la découverte de polymorphismes nucléotidiques variables.

Ces dernières années, le développement des études d'association pangénomique (GWAS : genome-wide association study) dont le but est d'analyser les liens entre les variations génétiques et les variations phénotypiques dans de larges cohortes a permis de mettre en avant l'effet protecteur ou délétère de certains polymorphismes nucléotidiques sur certaines pathologies. Les études d'association à l'échelle du génome sont utilisées pour effectuer des criblages impartiaux des génomes des individus à haut risque afin d'identifier les séquences de variants génétiques associées au risque de maladie. Les polymorphismes mono-nucléotidiques, définis comme un changement dans un seul nucléotide (adénine, thymine, cytosine ou guanine), sont les types les plus courants de variation génétique. Ainsi, les études d'association pangénomique ont permis d'identifier de nombreuses variations génétiques ayant un effet délétère ou protecteur dans la maladie coronaire. En particulier, certains polymorphismes des gènes codant pour le récepteur du LDL-R ou de l'apoliprotéine B sont associés à une clairance plus élevée du LDL-C, et donc à une exposition au cholestérol moindre sur le long cours (271) **(figure 9).** A l'inverse, certains variants génétiques sont associés au développement d'une maladie coronaire prématurée **(tableau 6),** en particulier lorsqu'ils concernent les gènes codant pour les voies de l'inflammation et du cholestérol (272, 273). L'inclusion de ces polymorphismes dans des scores de risque cardiovasculaire permet une meilleure détection théorique des individus à risque, bien qu'elle reste pour le moment peu exploitable dans la pratique clinique actuelle. En 2018, une analyse de 425 196 patients de l'étude UK Biobank visant à déterminer un score de risque génétique fondé sur 300 variants associés à la maladie coronaire prématurée a démontré qu'un large éventail de maladies cardiovasculaires, y compris prématurées, partageaient les mêmes racines génétiques, et augmentait la performance des scores de risque (274). Cependant, ces polymorphismes ou variants génétiques ne suffisent pas à expliquer à eux seuls la survenue de la maladie coronaire prématurée.

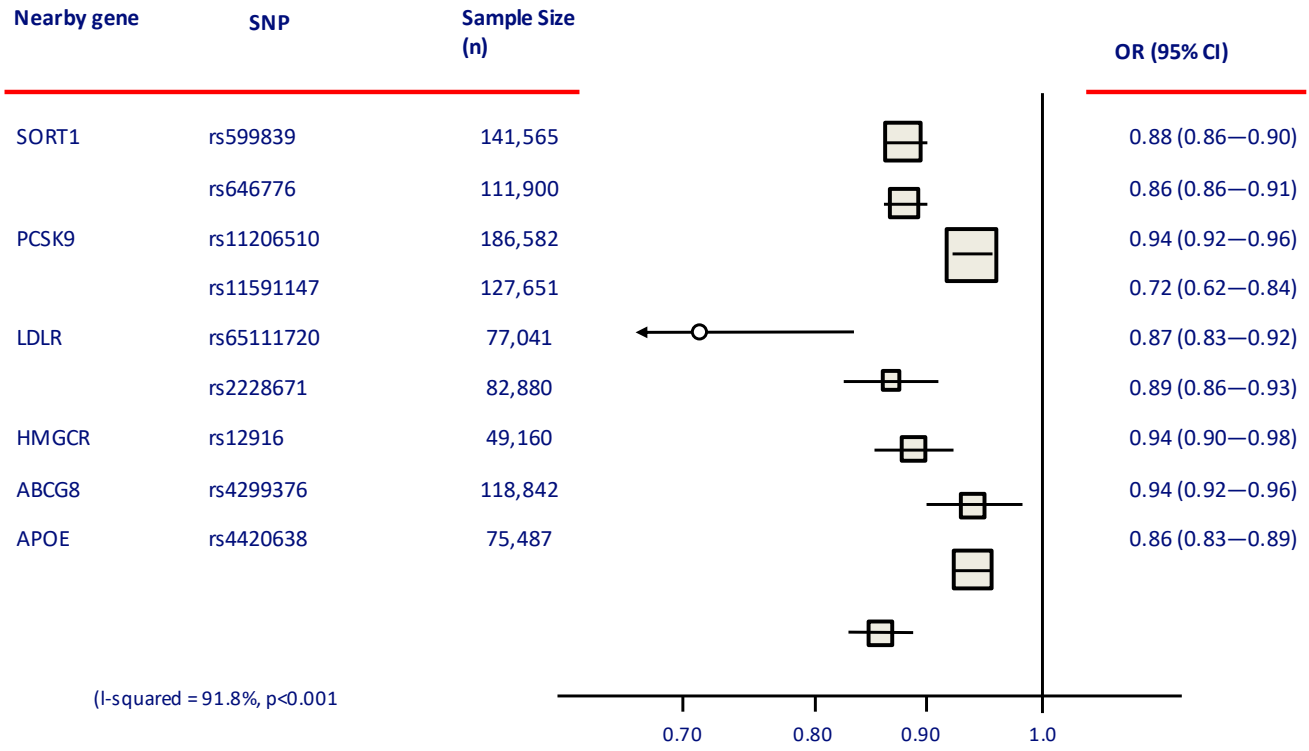


Figure 9. Méta-analyse de 312 321 individus avec 9 polymorphismes de 6 gènes impliqués dans une exposition à LDL-C bas sur le long terme.

Adapté de *Ference BA, et al. J Am Coll Cardiol. 2012;60:2631–9. (269)*

Tableau 6. Association entre variants génétiques et maladie coronaire.

Référence 269 : Assimes TL. Et al. *Genetics: Implications for Prevention and Management of Coronary Artery Disease*. J Am Coll Cardiol 2016;68(25):2797–818. Doi: 10.1016/j.jacc.2016.10.039. e

Référence 270 : Wang H. et al. *Pathogenesis of premature coronary artery disease: Focus on risk factors and genetic variants.* Genes & Diseases 2020. Doi: 10.1016/j.gendis.2020.11.003.

Gène impliqué	Chromosome	Polymorphisme	Risque de maladie coronaire (Odds Ratio)	Mécanisme impliqué
C6orf105	6	rs6903956	1.65	Inflammation
LPA	6	rs3798220	1.51	Lp(a)
9p21.3	9	rs4977574	1.29	Dysfonction endothéliale
C6orf10-BTNL2	6	rs9268402	1.16	Inflammation
LDL-R	19	rs1122608	1.14	Métabolisme du LDL-C
APOE	19	rs2075650	1.14	Métabolisme du LDL-C
ANGPTL4	19	rs116843064	1.14	Métabolisme des triglycérides
NOS3	7	rs3918226	1.14	Hypertension
APOA5	11	rs964184	1.13	Métabolisme des triglycérides
APOC3 11	11	rs964184	1.13	Métabolisme des triglycérides
CYP17A1-NT5C2	10	rs12413409	1.12	Hypertension
TTC32-WDR35	2	rs2123536	1.12	Inflammation
SORT1	1	rs599839	1.11	Métabolisme du LDL-C
LPL	8	rs264	1.11	Métabolisme des triglycérides
ATP2B1	12	rs7136259	1.11	Hypertension
ABO	9	rs579459	1.1	Métabolisme du LDL-C
PHACTR1	6	rs12526453	1.1	Inflammation
EDN1 6	10	rs12526453	1.1	Inflammation
ZC3HC1	7	rs11556924	1.09	Hypertension
PCSK9 1	1	rs11206510	1.08	Métabolisme du LDL-C
GUCY1A1	4	rs1842896	1.08	Inflammation
ADAMTS7	15	rs3825807	1.08	Dysfonction endothéliale
APOB	2	rs515135	1.07	Métabolisme du LDL-C
SH2B3	12	rs3184504	1.07	Hypertension
FURIN	15	rs17514846	1.07	Hypertension
ABCG5-ABCG8	2	rs6544713	1.06	Métabolisme du LDL-C
TRIB1	8	rs2954029	1.06	Métabolisme des triglycérides
ARHGAP42	11	rs7947761	1.04	Hypertension

2. Hérédité coronaire et hérédité des habitus : interaction gènes et environnement

L'hérédité forte constatée chez les individus atteints d'athérosclérose prématurée n'implique pas uniquement la transmission du patrimoine génétique, mais aussi celle des habitudes de vie, des facteurs de risques modifiables, des facteurs environnementaux et du stress psycho-social. Ainsi, une analyse subséquente de la UK Biobank a révélé que les facteurs de risque environnementaux étaient plus fréquents chez les patients ayant un score de risque génétique élevé, avec un surrisque significatif de développer une pathologie cardiovasculaire (**figure 10**) (148).

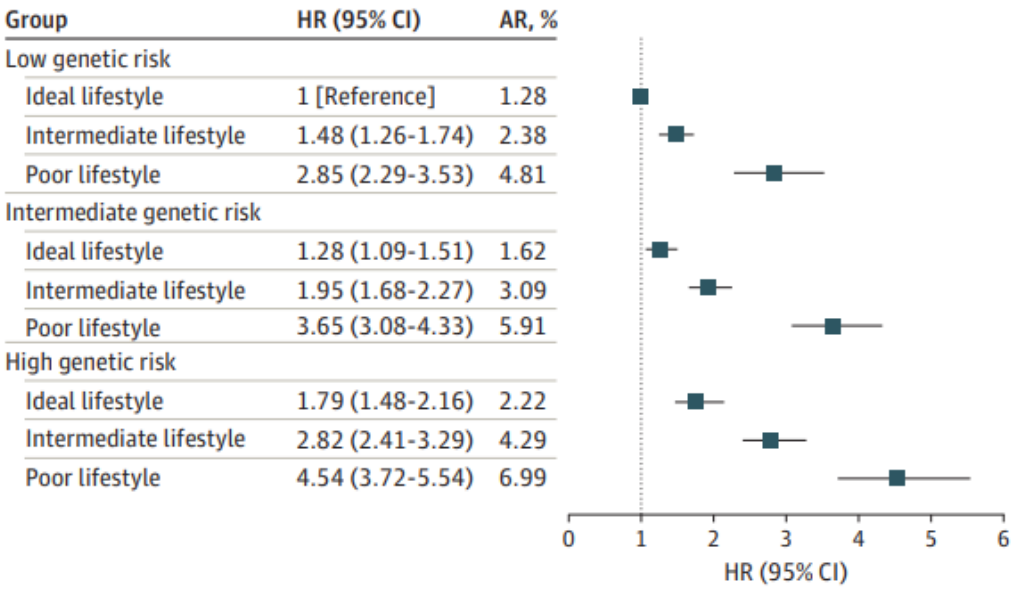


Figure 10. Contribution du style de vie et de la génétique dans la maladie coronaire (UK Biobank)

Adapté de *Said et al. Associations of Combined Genetic and Lifestyle Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study. JAMA Cardiol 2018;3(8):693–702.*

Cette interaction entre génétique et environnement a également été observée dans une étude de cohorte combinant 55685 individus des registres ARIC, de la Women's Genome Health Study et de la Malmö Diet and Cancer Sudy. Les facteurs de risque génétiques et les facteurs de risque liés au mode de vie étaient associés de manière indépendante à la survenue d'une maladie coronaire (**figure 11**) (89). Chez les patients ayant un style de vie sain, la présence d'un score génétique élevé multipliait le risque de développer une maladie coronaire par 2. Chez les patients ayant un score de risque génétique élevé, un mode de vie sain était associé à une diminution de 50 % du risque de développer un évènement coronaire.

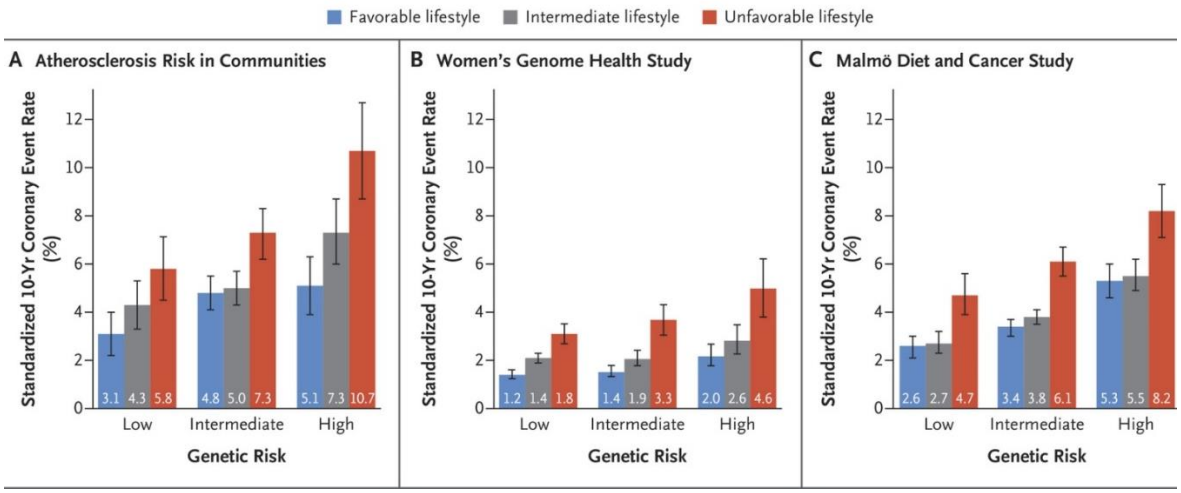


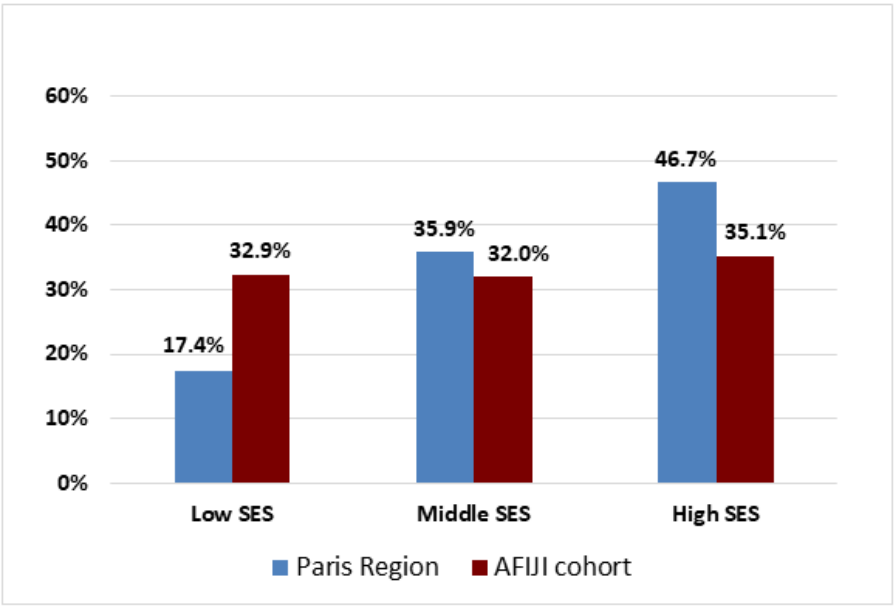
Figure 11. Contribution du style de vie et de la génétique dans la maladie coronaire (ARIC-WGHS-MDCS)

Adapté de *Khera AV., Emdin CA., Drake I., et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. N Engl J Med 2016;375(24):2349–58.*

L'importance du niveau socio-économique et sa contribution à l'établissement d'une maladie coronaire prématurée, ainsi qu'à son pronostic, a également été étudiée dans une analyse du registre AFIJI (en cours de soumission)(275). Sur la base des données INSEE publiées pour la région Ile-de-France, il a été observé une sur-représentation des patients ayant un niveau socio-économique faible dans le registre AFIJI en comparaison à la répartition locale (**figure 12**), avec une association sur le pronostic global. Ainsi, la présence d'une hérédité coronaire forte ouvre la

voie aux explorations génétiques, mais également aux explorations du style et des habitudes de vie mettant en jeu le pronostic cardiovasculaire.

A



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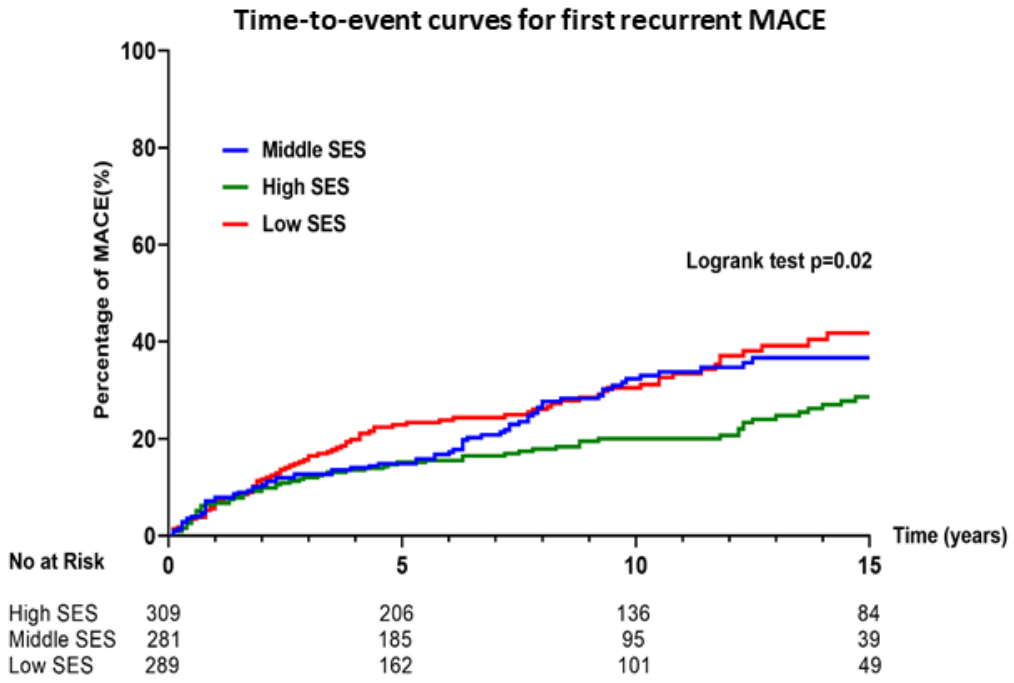

Figure 12. Répartition socio-économique du registre AFIJI en comparaison à la région Ile-de-France (A) et association entre niveau socio-économique et évènements cardiovasculaires (B).

Low SES = niveau socio-économique bas ; Middle SES = niveau socio-économique moyen ;

High SES = niveau socio-économique élevé

3. Syndrome métabolique : le patient américain est-il le patient français de demain ?

La comparaison des individus atteints dans le registre français mettait en évidence des patients ayant un taux de tabagisme bien plus élevé que chez les Américains (77,3 % versus 52,0 %) ainsi qu'un LDL-C moyen plus important (1,69 vs. 1,20 g/L) **(tableau 7).** Parmi les patients du registre français, 15 % présentaient un LDL-C supérieur à 1,9 g/dL, contre 5 % dans le registre américain.

Tableau 7 : Caractéristiques des patients des registres AFIJI et DCDD

	Registre AFIJI	**Registre DCDD**
Femmes	13.30%	27.50%
IMC moyen (kg/m²)	26.1	30
Tabagisme actif au moment du diagnostic	77.30%	52.00%
LDL-C moyen (g/L)	1.69	1.2
HTA	20.3%	23.8%
Hérédité coronaire	40.80%	39.80%
Diabète	10.70%	23.80%
Atteinte coronaire multiple	40.70%	40.40%

A l'inverse, les jeunes patients américains étaient plus souvent atteints de syndrome métabolique, d'obésité, d'hypertension, et de deux fois plus de diabète de type 2. Enfin, on comptait jusqu'à deux fois plus de femmes atteintes de maladie coronaire prématurée dans le registre américain en comparaison au registre AFIJI (27,5 % vs. 13,3%). Ces descriptions semblent importantes pour décrire les différents contributeurs de risque à la maladie coronaire, en particulier si on estime que les individus américains présentent les caractéristiques que présenteront les jeunes patients français dans quelques années : un tabagisme moins important, mais une plus grande proportion de syndrome métabolique et de femmes atteintes.

La progression du nombre d'individus atteints de syndrome métabolique en Europe et en France pourrait modifier le profil des patients atteints d'une maladie coronaire prématurée. Cette évolution doit pousser à l'implémentation de nouvelles stratégies de prise en charge des facteurs de risque cardiovasculaire, dépassant le simple cadre de l'arrêt du tabac et de la réduction du cholestérol, afin d'impliquer l'ensemble des marqueurs de risque concernés, y compris les risques psycho-sociaux (128, 232). L'obésité et le syndrome métabolique pourraient être les pourvoyeurs principaux de l'inflammation contribuant à l'athérosclérose prématurée. Cette hypothèse a été mise en évidence par l'analyse du biomarqueur GlycA dans plusieurs cohortes d'individus à risques : les individus ayant un syndrome métabolique présentaient une glycosylation des protéines de phase aigüe aussi élevée que ceux atteints de maladies inflammatoires chroniques auto-immunes ou de cancers. Cette inflammation chronique et associée à la genèse d'une athérosclérose prématurée était réversible si les mesures adéquates concernant les habitudes de vie, l'activité sportive et les facteurs de risques étaient mises en œuvre (276).

4. Evolution de l'athérosclérose coronaire prématurée

Dans les deux populations, les analyses angiographiques ont montré la présence de 40% de patients atteints de lésions pluri-tronculaires : dans le registre AFIJI, 20,6% avaient une maladie touchant deux artères coronaires au diagnostic et 18,9 % avaient d'emblée une maladie tritronculaire. Le registre DCDD retrouve des proportions similaires avec 24,1% et 16,2% de bi- et tritronculaires au diagnostic, respectivement. Dans le registre DCDD, la proportion d'atteintes multi-tronculaires augmentait avec l'âge observé : 28% chez les moins de 35 ans, 38% chez les patients entre 35 et 45 ans et 43% chez les patients entre 45 et 50 ans.

Le suivi angiographique de ces patients a révélé une évolution diffuse et rapide vers une pathologie coronaire multi-tronculaire, en particulier chez les patients ayant des facteurs de

risque non contrôlés. Alors que l'étude PROSPECT avait montré une évolution répartie de manière équilibrée entre récidives sur lésion coupable et néo-lésions chez les patients suivis après un infarctus du myocarde, le suivi angiographique AFIJI a démontré une évolution plus rapide vers les néo-lésions. Cette évolution diffuse de l'athérosclérose coronaire, avec des ruptures de plaques provoquant de nouveaux évènements thrombotiques, soutient l'hypothèse d'une pathologie chronique, voire systémique. Une étude de la banque d'imagerie d'AFIJI est en cours, montrant une fréquence élevée d'épaississement de l'intima-média des artères carotides et fémorales ainsi que la présence de plaques d'athérome.

5. Une pathologie évolutive grevée d'un mauvais pronostic

Les données de suivi d'AFIJI et de DCDD sont concordantes dans le caractère sévère du pronostic, avec un taux de mortalité élevé jusqu'à 20% à 10 ans – soit un patient sur 5 avant même l'âge moyen de développement de la pathologie. Ce suivi a également mis en lumière le nombre important de récidives d'évènements ischémiques liées à une évolution de l'athérosclérose coronaire ou même systémique avec l'apparition d'accidents vasculaires cérébraux. La mise en évidence de ce pronostic péjoratif est une avancée importante dans la compréhension de la maladie, car il contraste avec les publications initiales sur les jeunes patients pour lesquels un suivi court semblait révéler un pronostic « faussement rassurant » **(tableau 8).** Cette idée reçue a également été renforcée par les scores recommandés par la société de cardiologie comme le SCORE ou le 10-year ASCVD, dans lequel l'âge pèse beaucoup dans l'estimation du risque cardiovasculaire.

Tableau 8 : Caractéristiques des patients atteints de maladie coronaire en fonction des registres

	AFIJI <45 ans	DCDD < 50 ans	PROSPECT ACS/PCI	DAPT Study	Young-MI registry
Age moyen	40	45	58	62	45
SCA ST+ à l'admission	80%	38.6 %	96%	26%	57.4 %
Fumeurs actifs	77%	49.4 %	48%	21%	52.3 %
Diabète	11%	23.8 %	17%	31%	16.7 %
Atteinte multi tronculaire	39%	40.4 %	79%	NA	-
Taux d'évènement pour 100 patient-année	2.2	2.7	1.48	1.56	1.1

6. Contribution de l'inflammation à l'athérosclérose prématurée

La contribution de l'inflammation aux évènements cardiovasculaires a été validée depuis plusieurs années, notamment en utilisant la CRP-us, mais également d'autres marqueurs tels que l'IL-6 ou l' IL-1β (53, 171). Dans cette thèse, l'hypothèse était celle d'une contribution plus forte de l'inflammation chez les patients atteints d'une maladie coronaire prématurée en comparaison aux sujets développant une maladie coronaire à un âge standard. Cette hypothèse a été évaluée par la comparaison de l'association entre inflammation et maladie coronaire en fonction des âges en se référant au GlycA, ainsi qu'au pronostic post infarctus via l'étude de l' IL-1β. Le GlycA – véritable hémoglobine glyquée de l'inflammation - présente l'avantage de mesurer l'inflammation infraclinique et clinique, au long cours, en impliquant plusieurs voies des protéines de la phase aigüe de l'inflammation. Dans la sous-étude de l'essai clinique PROMISE, l'association entre GlycA et maladie coronaire chez des adultes sans antécédents particuliers était plus importante chez les patients jeunes que chez les patients plus âgés. La présence de cette inflammation infraclinique chez les patients jeunes est souvent l'expression d'un état de santé altéré par des habitudes de vie délétères (**figure 13**). L'exemple des patients souffrant d'un

syndrome métabolique est l'un des plus parlants : les patients présentant un IMC>30 kg/m^2 présentaient des niveaux de GlycA plus élevés. Pour rappel, le tissu adipeux est un organe endocrinien actif qui sécrète des cytokines contribuant à la résistance à l'insuline, à la dyslipidémie, à la coagulation et à l'inflammation. Une inflammation chronique de bas grade et une activation du système immunitaire sont souvent observées dans l'obésité et peuvent jouer un rôle causal dans le développement des maladies cardiovasculaires et du diabète de type 2. Ainsi, chez les patients souffrant d'obésité, les protéines de l'inflammation telles que l'haptoglobine, la transferrine ou la CRP-us sont souvent discrètement élevées (276–278).

Ces observations semblent également particulièrement importantes pour tenter de comprendre le mécanisme contribuant au pronostic plus défavorable observé chez les femmes dans la DCDD. Parmi les explications possibles, nous avons observé des niveaux de glycosylation – et donc d'inflammation infraclinique - plus élevés chez les femmes se présentant avec une maladie coronaire stable (67,8 % de femmes dans le quartile 4 de GlycA contre 41,3 % dans le quartile 1). Dans une étude incluant 819 patients ayant une maladie coronaire stable et 89 individus contrôles, les niveaux d'IL-6 étaient plus élevés chez les femmes ayant une maladie coronaire, et s'élevaient plus facilement lors d'un stress (279). Cette inflammation chronique contribue également au développement des marqueurs de risque cardiovasculaire nouvellement décrits chez les jeunes femmes, tels que la ménopause précoce, le diabète gestationnel et l'hypertension artérielle gravidique (280, 281). Ces données suggèrent ainsi que les femmes atteintes de maladie coronaire prématurée étaient le plus souvent atteintes de multiples facteurs de risque avec une altération des habitudes de vie plus importante.

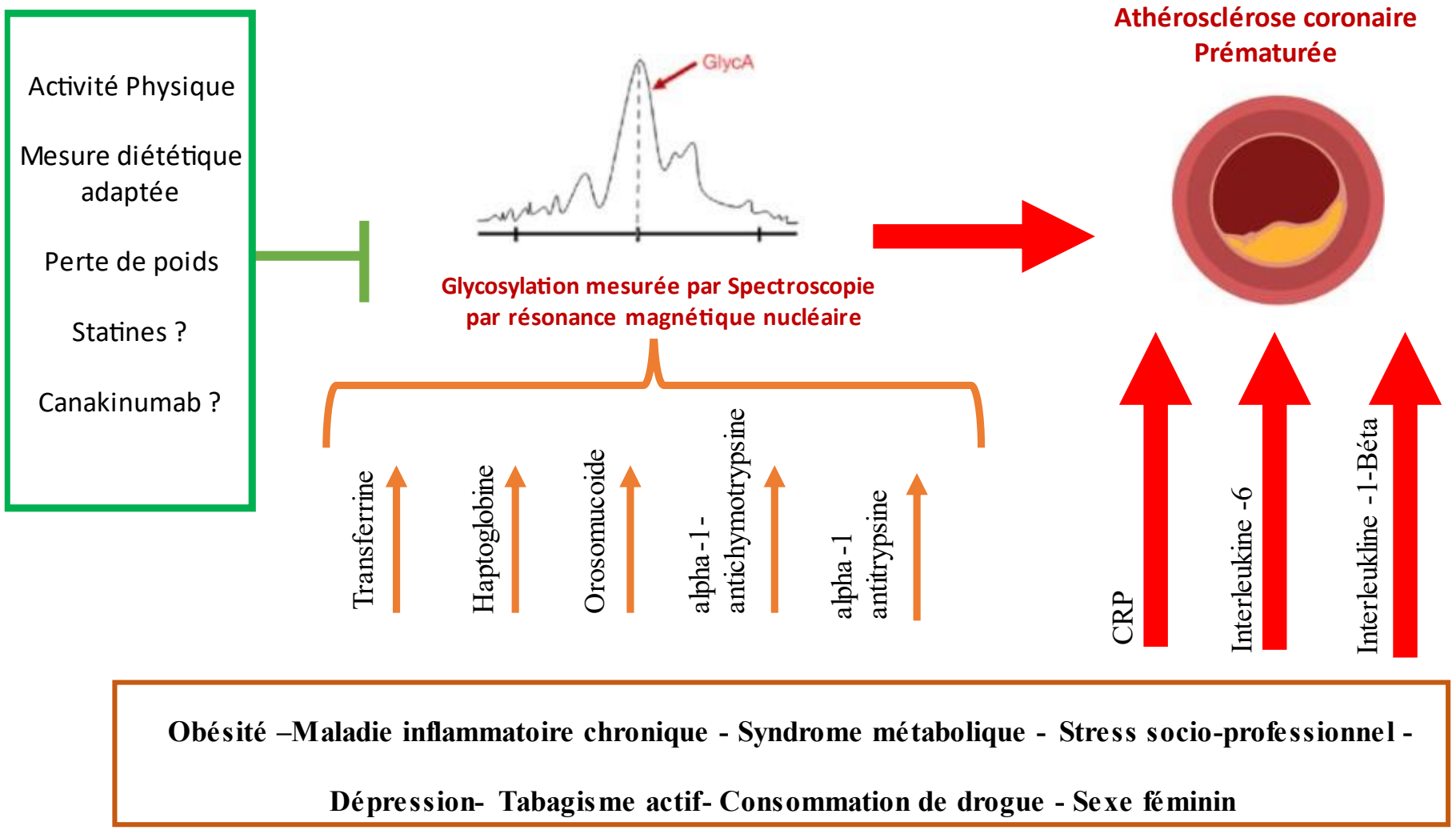

Figure 13. Contribution de l'inflammation à la maladie coronaire prématurée

La contribution de l'inflammation dans la genèse de l'athérosclérose précoce a également été mise en avant par l'étude des polymorphismes génétiques responsables de mutations des différentes protéines de l'inflammation (282, 283). Dans une étude de cohorte impliquant 100 individus du sous-continent indien âgés de 37 ans appariés avec des témoins, la présence d'un polymorphisme de l'IL-6 était associée à un surrisque de développer une maladie coronaire prématurée (284). Une association similaire a été décrite entre les polymorphismes génétiques codant pour les interleukines 17A et 35 et le risque de développer une maladie coronaire précoce (285, 286).

L'autre contribution de l'inflammation à la progression de la maladie athérothrombotique s'effectue par la persistance d'une réactivité plaquettaire élevée sous traitement optimal chez les patients atteints d'une maladie inflammatoire clinique ou infraclinique. De nombreuses études ont démontré que l'hyperréactivité plaquettaire sous traitement était associée à un surrisque d'évènement ischémique chez les patients traités en prévention secondaire d'un infarctus du myocarde ou d'une maladie coronaire stable (287–289). La présence d'une hyperréactivité plaquettaire sous traitement a souvent été observée chez les patients suivis pour une obésité ou un syndrome métabolique, représentant une proportion importante des jeunes individus atteints d'une maladie coronaire prématurée (290, 291). Elle a également été observée chez les patients atteints de maladies inflammatoires chroniques telles que le psoriasis, ou de pathologies entrainant des désordres immunitaire telles que le l'infection par le VIH (292). Dans l'étude EVERE 2 ST-HIV incluant des patients admis pour un infarctus du myocarde, la réactivité plaquettaire de 80 patients suivis pour un VIH a été comparée et appariée à celle de 160 patients sans VIH : les patients atteints de SCA infectés par le VIH présentaient des niveaux plus élevés de réactivité plaquettaire en réponse aux inhibiteurs de P2Y12 et à l'aspirine que les patients non-VIH, quel que soit le test utilisé.

7. Contribution de l’inflammation au cours de l’infarctus du myocarde

Lors de l’infarctus du myocarde, les myocytes lésées en apoptose vont induire la sécrétion de l’IL-1β menant au recrutement des leucocytes et à la coordination de la réponse inflammatoire (293). L’étude des concentrations d’IL-1β mesurées au moment de l’infarctus du myocarde dans le registre e-PARIS, ainsi que la démonstration de son association avec le pronostic à 90 jours et 1 an, constituent également des données importantes dans la compréhension du rôle de l’inflammation lors de la rupture de plaque puis dans le cadre du risque résiduel. Lors de la rupture de plaque, l'ampleur et l'intensité de la réponse inflammatoire sont en corrélation avec une taille supérieure de l'infarctus et un pronostic plus sombre à court terme, mais également sur le long terme à 1 an. Cette association était significative après ajustement sur les variables confondantes, démontrant l’implication des niveaux élevés d’IL-1β dans le pronostic à la phase précoce de rupture de plaque et de dommage myocardique, mais également dans le risque cardiovasculaire résiduel qu’ils traduisent. Il s’agit de la première étude à mesurer l’IL-1β dans l’infarctus du myocarde et à établir une véritable association pronostique, la plupart des études antérieures s’étant plutôt focalisées sur l’IL-6 (189).

8. Modulation de l’inflammation pour prévenir l’athérosclérose prématurée

La modulation de l’inflammation afin de prévenir l’athérosclérose prématurée et l’athérothrombose constitue donc une question cruciale, notamment depuis la publication de l’essai clinique CANTOS démontrant les effets du canakinumab sur la réduction des évènements cardiovasculaires (151). Plusieurs voies thérapeutiques ont été explorées afin d’évaluer la diminution de l’inflammation infraclinique ainsi que son effet potentiel sur les évènements cardiovasculaires.

Avant l’utilisation d’agents thérapeutiques médicamenteux, les différentes études ont montré que l’amélioration du style de vie, avec l’arrêt du tabac, la reprise de l’exercice physique

et la mise en œuvre d'un régime alimentaire adapté sont des moyens accessibles visant à diminuer l'inflammation. Dans une étude comprenant 1568 individus, l'implémentation de programmes d'exercice physique a permis de réduire le niveau de glycosylation des protéines inflammatoires, en particulier lorsqu'un programme diététique y était adjoint (294). Dans une autre étude comprenant 27 jeunes hispaniques – ayant une moyenne d'âge de 15 ans, souffrant d'obésité et de prédiabète – les programmes de diététique et d'exercice physique ont permis de réduire le taux de glycosylation circulante de moitié (276). Une réduction similaire du GlycA via l'implémentation d'exercice physique et d'un régime alimentaire a été observée chez 169 individus sédentaires atteints de prédiabète de type 2. De manière intéressante, cette réduction était également corrélée à la diminution de la graisse viscérale et sous cutanée chez ces patients (169).

L'observation de la contribution de l'inflammation au développement de la maladie coronaire prématurée soulève la question de la modulation de l'inflammation en prévention primaire. A ce titre, les dernières recommandations de l'ESC et de l'AHA/ACC ont intégré le dosage de la CRP-us dans l'évaluation du risque cardiovasculaire en prévention primaire. Néanmoins, celui-ci ne s'intègre qu'avec très peu de poids dans la décision de prescrire une statine en prévention primaire, tandis que leur effet chez ces patients a été clairement démontré même lorsque le LDL-C est bas (54, 295). Les statines restent pour l'heure la seule thérapie médicamenteuse ayant fait ses preuves en prévention primaire chez les patients présentant une inflammation infraclinique mesurée par CRP-us. La colchicine fait figure de voie prometteuse puisque son utilisation dans la goutte et dans les rhumatismes inflammatoires a également été associée à une diminution des évènements cardiovasculaires (296, 297). Néanmoins, il n'y a pour l'instant aucune étude randomisée sur le sujet ; l'étude COLCOT-T2D devrait randomiser 10 000 patients atteints d'un diabète de type 2 sans maladie cardiovasculaire établie.

9. Modulation de l'inflammation en prévention secondaire

La publication de l'essai clinique CANTOS a marqué un pas en avant dans la perspective d'interrompre l'évolution de l'athérosclérose en réduisant l'inflammation. Dans cette étude comprenant 10 061 patients ayant eu un infarctus du myocarde et présentant une CRP-us élevée, le canakinumab, anticorps monoclonal ciblant l'IL-1β, a réduit le taux d'événements cardiovasculaires de 20 % (298). Pour note, cette réduction est d'une amplitude similaire à la protection cardiovasculaire observée avec les inhibiteurs du PCSK9 ou les inhibiteurs du P2Y12. L'étude CANTOS faisait suite à des études expérimentales et pré-cliniques montrant un réel bénéfice de l'inhibition de l'IL-1β dans l'infarctus du myocarde, avec un effet sur la taille de l'infarctus et le remodelage de l'infarctus du myocarde (299). Les inhibiteurs de l'IL-6, tels que le tocilizumab, ont également montré des résultats prometteurs sur le remodelage myocardique et le pronostic cardiovasculaire (300, 301), de même que la colchicine dont l'effet est pléiotrope sur les marqueurs inflammatoires (134).

La modulation de l'inflammation sera en particulier étudiée dans le programme hospitalier de recherche clinique ALBORAN, qui évaluera l'inhibition de l'IL-1 β par l'Anakinra chez les patients admis pour une insuffisance cardiaque sévère avec une dysfonction ventriculaire gauche d'origine ischémique, ou non-ischémique.

10. Développement des outils d'imagerie pour mesurer l'âge vasculaire

L'étude 5 présentée dans cette thèse est un exemple d'approche translationnelle et intégrative permettant de mieux phénotyper les patients atteints d'athérosclérose prématurée, mais également de mieux stratifier leur risque cardiovasculaire sur le long terme.

L'analyse de la rigidité de l'aorte par IRM – à l'aide de nouveaux algorithmes d'imagerie - a permis de mettre en avant le caractère systémique de l'atteinte artérielle prématurée. Il s'agissait aussi d'évaluer une nouvelle modalité d'évaluation de l'athérosclérose artérielle,

technologiquement plus avancée que la mesure de l'onde de pouls ou que la mesure de l'épaisseur intima-média. En effet, l'hypothèse du caractère systémique de l'atteinte artérielle chez certaines familles de patients avec une maladie coronaire prématurée a tout d'abord été évaluée avec la mesure de l'onde de pouls. Dans une étude cas-témoins comprenant 50 patients avec une atteinte coronaire prématurée, 50 membres de leur famille au premier degré, et 50 témoins sains, des investigateurs danois avaient observé une rigidité vasculaire plus élevée chez les patients ayant l'atteinte coronaire et leurs apparentés (302). Les études menées sur la cohorte MESA chez l'adulte plus âgé, et l'étude 5 menée dans la cohorte AFIJI ont bien montré l'intérêt d'une évaluation intégrative du système artériel pour mieux prédire les évènements cardiovasculaires (87). Néanmoins, cette approche reste pour le moment expérimentale, et des données de recherche supplémentaires seront nécessaires pour l'intégrer comme un nouveau marqueur de risque menant à des adaptations thérapeutiques ou à un reclassement du risque des patients.

11. Détection des individus à risque de maladie coronaire prématurée

Les études 6 et 7 de cette thèse ont montré la faible efficacité des recommandations américaines et européennes sur la détection des individus à risque de maladie coronaire prématurée. Les recommandations ACC/AHA ne détectaient que 40% des patients qui feront un infarctus du myocarde avant l'âge de 55 ans et celles de l'ESC 2019 uniquement 16 % - en comparaison à près de 80% de détection des patients à risque de développer une maladie coronaire à un âge moyen **(tableau 9).**

Tableau 9 : Eligibilité aux statines avant un premier infarctus du myocarde selon les différentes recommandations

	Eligibilité aux statines (Classe I ou Classe IIa)	
	< 55 ans	**> 55 ans**
ACC/AHA 2018	39.40%	75%
ESC 2019	16.50%	75%
ESC 2021 (Nouveau SCORE2)	48.4 %	60 %

Cet échec souligne l'importance d'améliorer les algorithmes d'identification des jeunes adultes à risque de maladie coronaire, et d'adopter une approche multimodale avec une inclusion plus décisive des modificateurs de risque spécifiques. Pour note, si la mise à jour du score de risque cardiovasculaire de l'ESC par la mise au point du SCORE2 a permis d'améliorer la détection des jeunes individus à risque d'infarctus du myocarde, plus de 50 % ne sont toujours pas détectés (303). Sur la base de l'ensemble des études présentées dans cette thèse, voici plusieurs principes qui devraient s'appliquer dans cette population :

- Ne pas utiliser les scores de risque SCORE et ASCVD qui ne sont pas adaptés aux populations jeunes (139–141).
- Privilégier une approche comprenant les marqueurs de risque, en particulier la présence d'une CRP-us élevée, d'un syndrome métabolique ou d'une maladie inflammatoire chronique.
- Mesurer l'âge vasculaire par IRM aortique, mais également mesurer l'épaisseur média-intima.
- Intégrer la situation de prédiabète chez un patient jeune comme un très haut risque cardiovasculaire.
- Abaisser le seuil d'éligibilité pour une statine à 1,6 g/dL ; une simulation dans le registre DDCD et Young MI a démontré que cela améliorerait l'éligibilité de 20% (109).

- Mieux intégrer les marqueurs de risque socio-professionnels dans l'estimation du risque.
- Dépister systématiquement les apparentés au premier degré pour une maladie coronaire prématurée, avec un bilan du cholestérol, une échographie des troncs supra-aortiques et des artères des membres inférieurs, voire un coroscanner.

VII. CONCLUSIONS

Les travaux présentés dans cette thèse ont permis de décrire plus précisément le profil et la physiopathologie de l'athérosclérose prématurée. Les observations fondamentales qui ont été mises en évidence sont une pierre à l'immense édifice qu'il reste à bâtir pour ces patients. Les principales conclusions de cette thèse sont les suivantes :

1. L'importance des facteurs et des marqueurs de risque modifiables, dont le rôle et la prévalence semblent bien plus importants que les facteurs de risque non modifiables tels que l'hypercholestérolémie familiale, qui ne concernait que moins de 1% des individus.

2. Le caractère évolutif de l'athérosclérose prématurée, avec une atteinte rapidement multi tronculaire et systémique.

3. Le pronostic sévère de la maladie coronaire prématurée : un patient sur 5 décède dans les 10 ans, et plus de 50% ont des récidives ischémiques multiples. Ces premières observations sur le long terme contrastent fortement avec le court terme, rapportant un pronostic favorable.

4. L'importante contribution des pathologies inflammatoires et auto-immunes chroniques dans le mauvais pronostic des patients atteints d'une maladie coronaire prématurée.

5. Le lien fort qui existe entre athérosclérose prématurée et inflammation infraclinique chez les patients les plus jeunes. Cette association a été mise en avant par l'analyse de la glycosylation des protéines de la phase aiguë par le signal GlycA, véritable reflet de l'inflammation au long cours.

6. L'importante implication de l' IL-1β dans la cascade inflammatoire post infarctus du myocarde, et son association avec la mortalité à court et long terme.

7. La description de la rigidité aortique par IRM des patients atteints de maladie coronaire prématurée, et son association avec le pronostic cardiovasculaire.

8. Les faibles performances des recommandations américaines et européennes dans la détection et le traitement des individus à risque de développer une athérosclérose prématurée, et l'absence de directives spécifiques pour une prévention secondaire personnalisée et intensive une fois la maladie coronaire installée.

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IX. ANNEXES

Etude 1 : Page de couverture

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 15, 2019

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Long-Term Evolution of Premature Coronary Artery Disease

Jean-Philippe Collet, MD, PhD,[a,*] Michel Zeitouni, MD,[a,*] Niki Procopi, MD,[a] Jean-Sébastien Hulot, MD, PhD,[b] Johanne Silvain, MD, PhD,[a] Mathieu Kerneis, MD,[a] Daniel Thomas, MD,[a] Benoit Lattuca, MD,[a] Olivier Barthelemy, MD,[a] Yoan Lavie-Badie, MD,[c] Jean-Baptiste Esteve, MD,[d] Laurent Payot, MD,[e] Delphine Brugier, PhD,[a] Izolina Lopes, BSc,[a] Abdourahmane Diallo, PhD,[f] Eric Vicaut, MD, PhD,[f] Gilles Montalescot, MD, PhD,[a] for the ACTION Study Group

ABSTRACT

BACKGROUND The long-term evolution of premature coronary artery disease (CAD) is unknown.

OBJECTIVES The objective of this study was to describe the evolution of coronary atherosclerosis in young patients and identify the risk factors of poor outcomes.

METHODS Participants age ≤45 years with acute or stable obstructive CAD were prospectively enrolled and followed. The primary endpoint was all-cause death, myocardial infarction (MI), refractory angina requiring coronary revascularization, and ischemic stroke.

RESULTS Eight hundred-eighty patients with premature CAD were included. They were age 40.1 ± 5.7 years, mainly men, smokers, with a family history of CAD or hypercholesterolemia. At baseline presentation, 91.2% underwent coronary revascularization, predominantly for acute MI (78.8%). Over a follow-up of 20 years, one-third (n = 264) of patients presented with a total of 399 ischemic events, and 36% had at least a second recurrent event. MI was the most frequent first recurrent event (n = 131 of 264), mostly related to new coronary lesions (17.3% vs. 7.8%; p = 0.01; hazard ratio [HR]:1.45; 95% confidence interval [CI]: 1.09 to 1.93 for new vs. initial culprit lesion). All-cause death (n = 55; 6.3%) occurred at 8.4 years (median time). Ethnic origin (sub-Saharan African vs. Caucasian, adjusted hazard ratio [adjHR]: 1.95; 95% CI: 1.13 to 3.35; p = 0.02), inflammatory disease (adjHR: 1.58; 95% CI: 1.05 to 2.36; p = 0.03), and persistent smoking (adjHR: 2.32; 95% CI: 1.63 to 3.28; p < 0.01) were the strongest correlates of a first recurrent event. When considering all recurrent events, the same factors and Asian ethnicity predicted poor outcome, but persistent smoking had the greatest impact on prognosis.

CONCLUSIONS Premature CAD is an aggressive disease despite the currently recommended prevention measures, with high rates of recurrent events and mortality. Ethnicity and concomitant inflammatory disease are associated with poor prognoses, along with insufficient control of risk factors. (J Am Coll Cardiol 2019;74:1868–78)
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Etude 2 : Page de couverture

Journal of the American Heart Association

ORIGINAL RESEARCH

Risk Factor Burden and Long-Term Prognosis of Patients With Premature Coronary Artery Disease

Michel Zeitouni, MD; Robert M. Clare, MS; Karen Chiswell, PhD; Jawan Abdulrahim, MD; Nishant Shah, MD; Neha P. Pagidipati, MD; Svati H. Shah, MD, MHS; Matthew T. Roe, MD; Manesh R. Patel, MD; W. Schuyler Jones, MD

BACKGROUND: Coronary artery disease (CAD) is increasing among young adults. We aimed to describe the cardiovascular risk factors and long-term prognosis of premature CAD.

METHODS AND RESULTS: Using the Duke Databank for Cardiovascular Disease, we evaluated 3655 patients admitted between 1995 and 2013 with a first diagnosis of obstructive CAD before the age of 50 years. Major adverse cardiovascular events (MACEs), defined as the composite of death, myocardial infarction, stroke, or revascularization, were ascertained for up to 10 years. Cox proportional hazard regression models were used to assess associations with the rate of first recurrent event, and negative binomial log-linear regression was used for rate of multiple event recurrences. Past or current smoking was the most frequent cardiovascular factor (60.8%), followed by hypertension (52.8%) and family history of CAD (39.8%). Within a 10-year follow-up, 52.9% of patients had at least 1 MACE, 18.6% had at least 2 recurrent MACEs, and 7.9% had at least 3 recurrent MACEs, with death occurring in 20.9% of patients. Across follow-up, 31.7% to 37.2% of patients continued smoking, 81.7% to 89.3% had low-density lipoprotein cholesterol levels beyond the goal of 70 mg/dL, and 16% had new-onset diabetes mellitus. Female sex, diabetes mellitus, chronic kidney disease, multivessel disease, and chronic inflammatory disease were factors associated with recurrent MACEs.

CONCLUSIONS: Premature CAD is an aggressive disease with frequent ischemic recurrences and premature death. Individuals with premature CAD have a high proportion of modifiable cardiovascular risk factors, but failure to control them is frequently observed.

Etude 3 : Abstract Présenté à ACC 2020

ACC.20 TOGETHER WITH WORLD CONGRESS OF CARDIOLOGY

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JACC March 24, 2020
Volume 75, Issue 11

Acute and Stable Ischemic Heart Disease

A NOVEL INFLAMMATORY MARKER OF GLYCOSYLATED PROTEINS IS ASSOCIATED WITH CAD AND INCIDENT EVENTS AND DEMONSTRATES AGE EFFECTS IN THE PROMISE TRIAL

Poster Contributions
Posters Hall_Hall A
Monday, March 30, 2020, 12:30 p.m.-1:15 p.m.

Session Title: Acute and Stable Ischemic Heart Disease: Basic 8
Abstract Category: 01. Acute and Stable Ischemic Heart Disease: Basic
Presentation Number: 1467-186

Authors: *Michel Zeitouni, Stephanie N. Giamberardino, Robert McGarrah, Neha Pagidipati, Geoffrey S. Ginsburg, Udo Hoffmann, Ann Marie Navar, Pamela Douglas, Svati Shah, Duke Molecular Physiology Institute, Durham, NC, USA, Duke Clinical Research Institute, Durham, NC, USA*

Background: GlycA, a measure of glycosylated proteins, is a novel biomarker of chronic sub-clinical inflammation. Its association with premature coronary artery disease (CAD) is unknown.

Methods: GlycA data from the PROMISE trial were compared to incident cardiovascular (CV) events (death, myocardial infarction or unstable angina; n=4032) and prevalent obstructive CAD (stenosis>70% by core lab read CTA; n=1805). Interaction analyses evaluated age-effects: premature CAD (< 55 yo; n=519), early CAD (55 - 65 yo; n=811) and average-age CAD (>65 yo; n= 475). Linear regression and Cox proportional hazards modelling were adjusted for age, sex, diabetes, smoking status and hypertension.

Results: GlycA mean level was 455 μmol/l (SD 78). Patients with high GlycA levels were more frequently smokers, with diabetes and metabolic syndrome. GlycA was associated with obstructive CAD (adj OR 1.34, 95% [1.12 - 1.60] p<0.01 per 1 SD unit), with the strongest association for premature CAD (OR 1.76 [1.21-2.55], p<0.01) (figure). During a median follow-up of 2 years, GlycA was associated with incident CV events (adj HR 1.29 (per 1 SD), 95%CI, [1.10 - 1.51], p<0.01), and death (adj HR 1.56 [1.27 - 1.92], p<0.01), without interaction with age.

Conclusion: In patients with angina, higher levels of GlycA are associated with a higher prevalence of obstructive CAD and more incident CV events. The association with CAD was stronger in younger adults, highlighting the possible contribution of sub-clinical inflammation to premature CAD.

Etude 4 : Abstract présenté ESC 2020

Reduced proximal aortic distensibility is related to recurrent ischemic events in premature coronary artery disease

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Funding Acknowledgement: Type of funding source: None

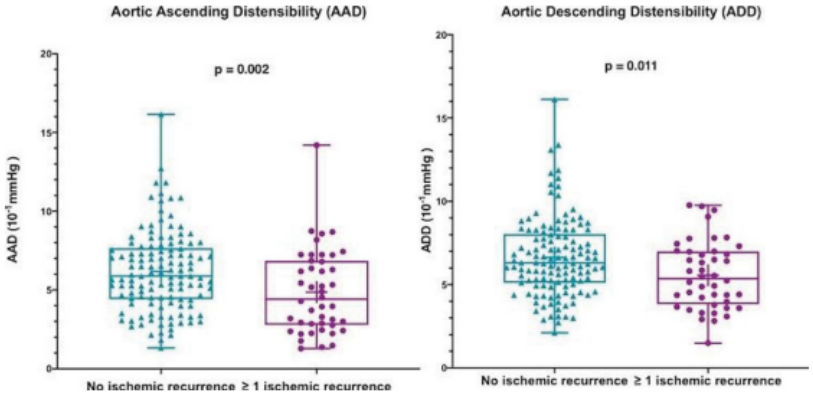
Background: Proximal aortic distensibility is predictive of incident cardiovascular events in individuals >45 years without overt cardiovascular disease. Whether this applies to patients with premature coronary artery disease (PCAD) is unknown.

Objectives: To report proximal aortic distensibility in patients with PCAD and its association with ischemic recurrences.

Methods: Patients <45 years with acute or stable obstructive CAD were prospectively enrolled in the Appraisal of risk Factors in Young Ischemic patients Justifying aggressive Intervention (AFIJI) registry. Proximal aortic distensibility was evaluated with 2 parameters in proximal aorta: Ascending (AAD) and descending (ADD) aortic distensibility. They were measured by MRI using a high-resolution cine SSFP and an artificial intelligence-based segmentation method combined with simultaneously acquired central pressures. Ischemic recurrences were defined as the composite of cardiovascular death, myocardial infarction (MI), refractory angina requiring coronary revascularization, and ischemic stroke.

Results: 170 patients with an MRI at a median time of 7.9 months after the qualifying events were enrolled and followed-up for a median time of 3.7 years [IQ1 2.0, IQ3 7.3]. They were mostly young (mean age 40.4±6.3 years) smoking (48.8%) males (90.0%). Major clinical presentation at diagnosis was MI (87.7%). At a median time of 2.0 years, one out of four patients had one or more ischemic recurrence (n=44, 25.9%). Left ventricular ejection fraction was preserved (median 55% [IQ1 50, IQ3 60]). The quartile of patients with the lowest AAD – i.e. with the stiffest aorta- (median AAD 2.9.10–1mmHg for the first quartile vs. 8.6.10–1mmHg for the fourth quartile), had more frequently dyslipidemia and chronic inflammatory disease (respectively 44.2% vs. 30.2% in the overall cohort and 9.3% vs. 4.1% in the overall cohort). Multivessel PCAD was also more often in the first quartile distensibility patients (46.5% vs. 35.3% in the overall cohort). AAD and ADD were significantly lower for patients who presented ischemic recurrence than for those without ischemic recurrence (median 4.4 [2.8, 6.8].10–1mmHg vs. 5.9 [4.4, 7.6].10–1mmHg, p=0.002, and 5.4 [3.9, 7.0].10–1 mmHg vs. 6.3 [5.1, 8.0].10–1 mmHg, p=0.011 respectively). Reduced AAD and ADD were both associated with the occurrence of ischemic reccurrence in univariate analysis and after adjustment on age, mean central blood pressure and traditional cardiovascular risk factors (for AAD: crude OR 0.8 per 10–1mmHg, CI 95% [0.69,0.94] and adjusted OR 0.74 per 10–1mmHg CI 95% [0.56,0.89]; for ADD: crude OR 0.79 per 10–1mmHg CI 95% [0.66,0.94] and adj OR 0.76 per 10–1mmHg CI 95% [0.59,0.97]).

Conclusion: Reduced proximal aorta distensibility is associated with multivessel disease and ischemic recurrences, independently from age and traditional cardiovascular risk factors in patients <45 years with PCAD.



AAD and ADD according to recurrence

Etude 5: page de couverture

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 15, 2020

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Interleukin-1β and Risk of Premature Death in Patients With Myocardial Infarction

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ABSTRACT

BACKGROUND Inhibition of the interleukin (IL)-1β innate immunity pathway is associated with anti-inflammatory effects and a reduced risk of recurrent cardiovascular events in stable patients with previous myocardial infarction (MI) and elevated high-sensitivity C-reactive protein (hs-CRP).

OBJECTIVES This study assessed the association between IL-1β level with all-cause mortality in patients with acute ST-segment elevation MI who underwent primary percutaneous coronary intervention and the interplay between IL-1β and hs-CRP concentrations on the risk of premature death.

METHODS IL-1β concentration was measured in 1,398 patients with ST-segment elevation MI who enrolled in a prospective cohort. Crude and hazard ratios for all-cause and cardiovascular mortality were analyzed at 90 days and 1 year using multivariate Cox proportional regression analysis. Major adverse cardiovascular events (MACEs) were analyzed.

RESULTS IL-1β concentration measured at admission was associated with all-cause mortality at 90 days (adjusted hazard ratio [adjHR]: 1.47 per 1 SD increase; 95% confidence interval [CI]: 1.16 to 1.87; $p < 0.002$). The relation was nonlinear, and the highest tertile of IL-1β was associated with higher mortality rates at 90 days (adjHR: 2.78; 95% CI: 1.61 to 4.79; $p = 0.0002$) and at 1 year (adjHR: 1.93; 95% CI: 1.21 to 3.06; $p = 0.005$), regardless of the hs-CRP concentration. Significant relationships were equally observed when considering cardiovascular mortality and MACEs at 90 days (adjHR: 2.42; 95% CI: 1.36 to 4.28; $p = 0.002$, and adjHR: 2.29; 95% CI: 1.31 to 4.01; $p = 0.004$, respectively) and at 1 year (adjHR: 2.32; 95% CI: 1.36 to 3.97; $p = 0.002$, and adjHR: 2.35; 95% CI: 1.39 to 3.96; $p = 0.001$, respectively).

CONCLUSIONS IL-1β measured at admission in patients with acute MI was independently associated with the risk of mortality and recurrent MACEs. (J Am Coll Cardiol 2020;76:1763–73) © 2020 by the American College of Cardiology Foundation.

Etude 6: page de couverture

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 6, 2020

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Performance of Guideline Recommendations for Prevention of Myocardial Infarction in Young Adults

Michel Zeitouni, MD, MS, Michael G. Nanna, MD, Jie-Lena Sun, MS, Karen Chiswell, PhD, Eric D. Peterson, MD, MPH, Ann Marie Navar, MD, PhD

ABSTRACT

BACKGROUND The 2018 cholesterol guidelines of the American Heart Association and the American College of Cardiology (AHA/ACC) changed 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statin) eligibility criteria for primary prevention to include multiple risk enhancers and novel intensive lipid-lowering therapies for secondary prevention.

OBJECTIVES This study sought to determine how guideline changes affected identification for preventive therapy in young adults with premature myocardial infarction (MI).

METHODS The study identified adults presenting with first MI at Duke University Medical Center in Durham, North Carolina. Statin therapy eligibility was determined using the 2013 ACC/AHA and 2018 AHA/ACC guidelines criteria. The study also determined potential eligibility for intensive lipid-lowering therapies (very high risk) under the 2018 AHA/ACC guidelines, by assessing the composite of all-cause death, recurrent MI, or stroke rates in adults considered "very high risk" versus not.

RESULTS Among 6,639 patients with MI, 41% were <55 years of age ("younger"), 35% were 55 to 65 years of age ("middle-aged"), and 24% were 66 to 75 years of age ("older"). Younger adults were more frequently smokers (52% vs. 38% vs. 22%, respectively) and obese (42% vs. 34% vs. 31%, respectively), with metabolic syndrome (21% vs. 19% vs. 17%, respectively) and higher low-density lipoprotein cholesterol (117 vs. 107 vs. 103 mg/dl, respectively) (p trend <0.01 for all). Pre-MI, fewer younger adults met guideline indications for 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statin) therapy than middle-aged and older adults. The 2018 guideline identified fewer younger adults eligible for statin therapy at the time of their MI than the 2013 guideline (46.4% vs. 56.7%; $p < 0.01$). Younger patients less frequently met very high-risk criteria for intensive secondary prevention lipid-lowering therapy (28.3% vs. 40.0% vs. 81.4%, respectively; $p < 0.01$). Over a median 8 years of follow-up, very high-risk criteria were associated with increased risk of major adverse cardiovascular events in individuals <55 years of age (hazard ratio: 2.09; 95% confidence interval: 1.82 to 2.41; $p < 0.001$), as was the case in older age groups (p interaction = 0.54).

CONCLUSIONS Most younger patients with premature MI are not identified as statin candidates before their event on the basis of the 2018 guidelines, and most patients with premature MI are not recommended for intensive post-MI lipid management. (J Am Coll Cardiol 2020;76:653-64) © 2020 by the American College of Cardiology Foundation.

Etude 7: page de couverture

ESC European Society of Cardiology

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CURRENT OPINION
Lipids

2019 ESC/EAS Guidelines for management of dyslipidaemia: strengths and limitations

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In 2019, the European Society of Cardiology and European Atherosclerosis Society released a new guideline document with substantial changes regarding the assessment of cardiovascular risk and treatments. The update of high-risk criteria and categories led to a better detection and primary prevention of patients at risk of a first cardiovascular event. Nonetheless, additional efforts are needed for a better inclusion of risk modifiers, especially specific to women, to improve risk stratification and direct primary prevention. Eventually, we discuss how these new guidelines implement PCSK9 inhibitors for very high-risk individuals and the evidence supporting new low-density lipoprotein cholesterol goals below, such as 55 and 40 mg/dL.

Keywords Dyslipidaemia • Guidelines • Statins • PCSSK9 inhibitors

X. PRODUCTION SCIENTIFIQUE PENDANT LA THESE

(Septembre 2018 – septembre 2021)

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XI. RESUME

Athérosclérose coronaire prématurée : facteurs de risque, pronostic, prévention et nouvelles approches mécanistiques.

Résumé: Cette thèse s'est intéressée à la question de l'athérosclérose coronaire prématurée, du profil clinique et biologique des individus qui en sont touchés, avec une approche physiopathologique permettant d'évaluer la contribution de l'inflammation et l'âge vasculaire. Les études 1 et 2 ont décrit le profil cardiovasculaire à très haut risque de ces patients et les facteurs d'évolution péjorative sur le long-terme. Ces études ont démontré que l'athérosclérose coronaire est une maladie évolutive avec une atteinte multi artérielle rapide, menant à un taux de mortalité de 20 % sur 10 ans. L'étude 3 a démontré la contribution importante de l'inflammation infraclinique dans la genèse de l'athérosclérose coronaire chez les individus les plus jeunes, en comparaison avec les populations plus âgées. Cette observation a pu être effectuée grâce à l'utilisation d'un nouveau biomarqueur de l'inflammation chronique le GlycA, signal composite de la glycosylation des protéines de phase aiguë. L'étude 4 a mis en avant l'importante implication de l' IL-1β dans la cascade inflammatoire post infarctus du myocarde, et son association avec la mortalité à court et long terme. L'étude 5 a évalué la rigidité de la racine de l'aorte mesurée en IRM comme nouveau marqueur de risque de la maladie coronaire prématurée, en ouvrant la voie vers une mesure intégrative du vieillissement vasculaire. Les études 6 et 7 ont mis en évidence la difficulté qu'ont les recommandations internationales américaines et européennes à détecter et traiter les individus à haut risque d'athérosclérose prématurés, et les opportunités manquées de traitement intensif après un premier infarctus du myocarde prématuré.

Mots clés : athérosclérose coronaire prématurée; facteurs de risque cardiovasculaire; inflammation ; rigidité aortique

Premature coronary atherosclerosis: risk factors, prognosis, prevention, and novel mechanistic approaches.

Abstract: This thesis focused on premature coronary atherosclerosis, the clinical and biological profile of affected individuals, with a pathophysiological approach aiming to assess the contribution of inflammation and vascular age. Studies 1 and 2 described the very high-risk cardiovascular profile of these patients and the factors of poor long-term outcomes. These studies have demonstrated that premature coronary atherosclerosis is a progressive disease with a rapid multi-arterial involvement, leading to a mortality rate of 20% over 10 years. Study 3 demonstrated the significant contribution of subclinical inflammation to the genesis of coronary atherosclerosis in younger individuals, compared with older populations. This observation relied on the use of a new biomarker of chronic inflammation, GlycA, a composite signal of the glycosylation of proteins in the acute phase. Study 4 demonstrated the significant involvement of IL-1β in the post-myocardial infarction inflammatory cascade, and its association with short and long-term death. Study 5 evaluated the stiffness of the aortic root measured by MRI as a new risk marker for premature coronary artery disease, introduction a new tool for an integrative measure of vascular aging. Studies 6 and 7 have highlighted the lack of performance of American and European international guidelines in detecting and treating individuals at high risk of premature atherosclerosis, and the missed opportunities for intensive treatment after a first myocardial infarction. premature.

Keywords : premature coronary atherosclerosis ; cardiovascular risk factors ; inflammation ; aortic stiffness