



**HAL**  
open science

## **Prevalence of familial hypercholesterolaemia in patients presenting with premature acute coronary syndrome**

Marie Hauguel-Moreau, Vincent Aïdan, Hélène Hergault, Alain Beauchet, Marion Pépin, Giulio Prati, Rémy Pillière, Mounir Ouadahi, Loïc Josseran, Christophe Rodon, et al.

### ► **To cite this version:**

Marie Hauguel-Moreau, Vincent Aïdan, Hélène Hergault, Alain Beauchet, Marion Pépin, et al.. Prevalence of familial hypercholesterolaemia in patients presenting with premature acute coronary syndrome. Archives of cardiovascular diseases, 2022, 115 (2), pp.87-95. 10.1016/j.acvd.2021.11.005 . hal-04006296

**HAL Id: hal-04006296**

**<https://hal.science/hal-04006296v1>**

Submitted on 22 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

## Prevalence of familial hypercholesterolaemia in patients presenting with premature acute coronary syndrome

**Abbreviated title:** Prevalence of FH in patients with premature ACS

**Tweet:** In a study including 457 pts with premature myocardial infarction (MI) and 9900 healthy subjects (<50yo), prevalence of familial hypercholesterolemia (FH) was 39 times greater among pts with premature MI. FH strongly associated with MI (aOR 38.4, 95% CI 19.1-79.4) [Add graphical abstract]

**Marie Hauguel-Moreau<sup>a,b,\*</sup>, Vincent Aïdan<sup>a,b</sup>, Hélène Hergault<sup>a,b</sup>, Alain Beauchet<sup>c</sup>, Marion Pépin<sup>b,d</sup>, Giulio Prati<sup>a,b</sup>, Rémy Pillière<sup>a,b</sup>, Mounir Ouadahi<sup>a,b</sup>, Loïc Josseran<sup>e</sup>, Christophe Rodon<sup>f</sup>, Jean-Pierre Rabès<sup>g</sup>, Philippe Charron<sup>h,i</sup> Olivier Dubourg<sup>a,b</sup>, Ziad Massy<sup>b,i</sup>, Nicolas Mansencal<sup>a,b</sup>**

<sup>a</sup> *Department of Cardiology, Ambroise Paré Hospital, AP-HP, Centre de Référence des Cardiomyopathies et des Troubles du Rythme Cardiaque Héritaires ou Rares, UVSQ, 92100 Boulogne-Billancourt, France*

<sup>b</sup> *INSERM U-1018, CESP, Épidémiologie Clinique, UVSQ, 94805 Villejuif, France*

<sup>c</sup> *Public Health Department, Ambroise Paré Hospital, AP-HP, UVSQ, 92100 Boulogne-Billancourt, France*

<sup>d</sup> *Department of Geriatrics, Ambroise Paré Hospital, AP-HP, UVSQ, 92100 Boulogne-Billancourt, France*

<sup>e</sup> *Département Hospitalier d'Epidémiologie et de Santé Publique, Hôpital Raymond-Poincaré, AP-HP, GHU Paris-Saclay, 92380 Garches, France*

<sup>f</sup> *Local Health Insurance, Hauts de Seine, 92000 Nanterre, France*

<sup>g</sup> *Laboratory of Biochemistry and Molecular Genetics, Ambroise Paré Hospital, AP-HP, Université Paris-Saclay, 92100 Boulogne-Billancourt, France*

<sup>h</sup> *Unité de Génétique Médicale, Centre de Référence des Maladies Cardiaques Héritaires ou Rares, Ambroise Paré Hospital, AP-HP, 92100 Boulogne-Billancourt, France*

<sup>i</sup> *Sorbonne Université, INSERM, UMR\_S 1166 and ICAN Institute for Cardiometabolism and Nutrition, 75013 Paris, France*

*i Department of Nephrology, Ambroise Paré Hospital, AP-HP, UVSQ, 92100 Boulogne-Billancourt, France*

\* Corresponding author at: Service de Cardiologie, ACTION Study Group, Hôpital Universitaire Ambroise Paré, AP-HP, Université Versailles-Saint Quentin, 9 avenue Charles de Gaulle, 92100 Boulogne-Billancourt, France.

*E-mail address:* marie.hauguel@aphp.fr (M. Hauguel-Moreau).

*Twitter address:* @NMansencal

## Summary

*Background.* – Familial hypercholesterolaemia (FH) is responsible for severe hypercholesterolaemia and premature cardiovascular morbidity and mortality. The first clinical event is typically an acute coronary syndrome. Unfortunately, FH is largely underdiagnosed in the general population.

*Aims.* – To assess the prevalence of clinical FH among patients with premature (aged ≤ 50 years) acute myocardial infarction (MI) and compare it with FH prevalence in a control population.

*Methods.* – We reviewed in our database all patients with premature MI (aged ≤ 50 years) referred to Ambroise Paré Hospital from 2014 to 2018. FH prevalence was estimated via the Dutch Lipid Clinic Network score, based on personal and family history of premature cardiovascular disease and low-density lipoprotein cholesterol concentrations. FH was “possible” with a score between 3 and 5 points, “probable” with a score between 6 and 8 and “definite” with a score above 8. FH prevalence in young patients with MI was then compared with FH prevalence in a general population of the same age from the CARVAR 92 prospective cohort.

*Results.* – Of the 457 patients with premature MI, 29 (6%) had “probable” or “definite” FH. In the CARVAR 92 cohort, 16 (0.16%) of 9900 subjects aged ≤ 50 years had “probable” or “definite” FH. FH prevalence was 39 times greater among patients with premature MI than in the control population ( $P < 0.0001$ ). In multivariable analysis, FH was strongly associated with MI (adjusted odds ratio 38.4, 95% confidence interval 19.1–79.4).

*Conclusions.* – FH is > 30-fold more common in patients referred for premature MI than in the general population; this highlights the need for FH screening after a first MI to enhance lipid-lowering therapy and allow early identification of family members.

## Résumé

*Contexte.* – L'hypercholestérolémie familiale est responsable d'une hypercholestérolémie sévère et d'une morbi-mortalité cardiovasculaire prématurée. Malheureusement, l'hypercholestérolémie est largement sous-diagnostiquée.

*Objectif.* – L'objectif était de calculer la prévalence de l'hypercholestérolémie familiale (HF) clinique parmi des patients ayant fait un infarctus du myocarde (IDM) avant 50 ans et de la comparer à la prévalence de l'HF dans la population générale.

*Méthodes.* – Les patients < 50 ans admis pour un IDM au CHU Ambroise Paré entre 2014 et 2018 ont été inclus. La prévalence de l'HF a été calculée en utilisant le score de Dutch incluant les antécédents personnels et familiaux de maladie cardiovasculaire prématurée et le taux de LDL cholestérol. L'HF était « possible » avec un score entre 3 et 5, « probable » avec un score entre 6 et 8 et « certaine » avec un score supérieur à 8. La prévalence de l'HF chez ces jeunes coronariens était ensuite comparée à la prévalence dans une population contrôle du même âge, issue de la cohorte CARVAR 92.

*Résultats.* – Parmi les 457 patients admis pour un IDM précoce, 29 (6 %) avaient une HF « probable » ou « certaine ». Dans la cohorte CARVAR 92, 16 (0,16 %) parmi 9900 sujets < 50 ans avaient une HF « probable » ou « certaine ». La prévalence de l'HF était 39 fois plus grande chez les jeunes coronariens que dans la population contrôle ( $P < 0,0001$ ). En analyse multivariée, l'HF était fortement associée à la survenue d'un IDM précoce (aOR 38,4, IC95 % 19,1–79,4).

*Conclusion.* – L'HF est > 30 fois plus fréquente chez les patients admis pour un IDM prématuré qu'en population générale.

## **KEYWORDS**

Familial hypercholesterolaemia;  
Dutch Lipid Clinic Network score;  
Acute myocardial infarction;  
Epidemiology

## **MOTS CLÉS**

Hypercholestérolémie familiale ;  
Score de Dutch ;  
Infarctus du myocarde aigu ;  
Épidémiologie

*Abbreviations:* ACS, acute coronary syndrome; CI, confidence interval; CVD, cardiovascular disease; DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolaemia; LDL-C, low-density

lipoprotein cholesterol; MI, myocardial infarction; OR: odds ratio; PCSK9, proprotein convertase subtilisin/kexin 9.

## Background

Familial hypercholesterolaemia (FH) is a common genetic disorder with an estimated prevalence of 1 in 500 to 1 in 200 in the general population [1-6]. FH is responsible for severe hypercholesterolaemia and premature cardiovascular morbidity and mortality [7, 8]. The first clinical event is typically an acute coronary syndrome (ACS). Unfortunately, FH is largely underdiagnosed in the general population [6, 9]. A screening strategy for the identification of FH among patients who experience a first episode of premature ACS is of importance. The Dutch Lipid Clinic Network (DLCN) score is a validated diagnosis algorithm based on personal and family history of premature cardiovascular disease (CVD), physical examination, low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations and molecular genetic testing, estimating the probability of FH [6]. Appropriate lipid-lowering treatment (high-dose statin, ezetimibe, proprotein convertase subtilisin/kexin 9 [PCSK9] inhibitor), close follow-up and cascade screening of relatives are required for patients newly diagnosed with FH [10]. However, FH prevalence in patients who experience premature ACS ranges from 5% to 50%, depending on the study [11-17].

In the present study, we assessed the prevalence of clinical FH among patients with premature acute myocardial infarction (MI), and compared it with FH prevalence in a control population of the same age, from the same population pool.

## Methods

### Study populations

Two populations were identified in this study: patients who experienced premature MI (“patients with premature MI” group); and a control population of subjects included in a large-scale screening campaign (“CARVAR 92 cohort” group).

### Patients with premature MI

We reviewed in our database all patients referred to Ambroise Paré University Hospital from 01 January 2014 to 31 December 2018 for type I premature MI (aged  $\geq$  50 years). Type I MI was defined as follows [18]: detection of a rise and/or fall in cardiac troponin concentration, with at least one value above the 99th percentile upper reference limit, and at least one of the following: (1) symptoms of acute MI; (2) new ischaemic electrocardiogram changes; (3) development of pathological Q waves; (4)

imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; and (5) identification of a coronary thrombus by coronary angiography. Data regarding cardiovascular risk factors (definitions are given in the [Appendix](#)), personal and family history of CVD, clinical presentation and lipid profile at admission, medication at admission and discharge and angiographic and revascularization data were assessed systematically.

### **Subjects aged $\leq$ 50 years from the CARVAR 92 cohort**

Between January 2007 and December 2018, we conducted a cardiovascular risk factor screening campaign in the western suburbs of Paris (the CARVAR 92 study) [19, 20]. The target population was subjects without known CVD aged between 40 and 70 years. In the present study, we only focused on subjects aged  $\leq$  50 years, corresponding to the control population. Socially insured inhabitants of the western suburbs of Paris matching the age requirement were sent a form inviting them to a free medical visit at one of the participating centres ( $n = 17$ ). The following details were systematically recorded: personal and family history of CVD, current cigarette smoking and any medication. A medical examination was performed. Screening included blood tests for total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglycerides and glucose, with 12 hours of fasting before the blood draw using standardized methods. All cardiovascular risk factors were systematically assessed [20]. A medical report was given to the participants and sent to their general practitioners. Educational and information purposes were systematically delivered. The study was approved by the National Commission for Data Protection and Liberties (CNIL France) and the Institutional Data Protection Authority of Paris-Saclay University Hospitals. All patients gave written informed consent.

### **Prevalence of FH**

We assessed FH prevalence by calculating a simplified DLCN score as in previous studies [15, 21-23] based on the following criteria: personal and family history of premature CVD ( $< 55$  years for men,  $< 60$  years for women), and LDL-C concentrations. For patients using lipid-lowering therapy at admission, we estimated untreated LDL-C concentrations based on type and dose of lipid-lowering therapy, applying a correcting factor for LDL-C adapted to the reported efficacy of each drug as done previously for similar analyses [15, 24, 25]. FH was “possible” with a score between 3 and 5 points,



“probable” with a score between 6 and 8 or “definite” with a score above 8; no FH was defined as a score < 3. FH was strongly suspected in the case of “probable” or “definite” FH. Prevalence of FH was calculated using the DLCN score for both populations and then compared.

## Statistical analysis

Quantitative data are expressed as means  $\pm$  standard deviations and qualitative data as frequencies and percentages. Analysis of variance and  $\chi^2$  tests were used for comparisons of characteristics between those with no FH, “possible” FH or “probable” or “definite” FH. To assess the association between premature MI and FH, we performed a multivariable analysis using a logistic regression model. The association between premature MI and traditional cardiovascular risk factors (sex, diabetes mellitus, high blood pressure, current smoking status, family history of premature CVD) has been demonstrated previously [26]. For that reason, we included in the logistic regression model those relevant confounding factors. The results are interpreted in terms of adjusted odd ratios (ORs) with their associated 95% confidence intervals (CIs). A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed with R Development Core Team (2019) (R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patients with premature MI

Between January 2014 and December 2018, we retrospectively included 465 consecutive patients referred for premature MI. We excluded eight patients because of missing LDL-C data. The final sample size was 457 (Fig. 1). Baseline characteristics of patients with type I premature MI with respect to FH diagnosis are presented in Table 1. Mean age was 44.7 years (male sex, 86%) and 66% had ST-segment elevation MI. Among the 457 patients with premature MI, 220 (48%, 95% CI 43–53%) had no FH, 208 (46%, 95% CI 41–50%) had “possible” FH and 29 (6%, 95% CI 4–9%) had “probable” or “definite” FH using the DLCN score. No significant difference was observed between patients with or without suspected FH, except for higher rates of antiplatelet therapy (*P* = 0.002) and lipid-lowering therapy (*P* < 0.001) at admission, as well as higher ezetimibe treatment at discharge (*P* < 0.001) in

patients with “probable” or “definite” FH. Post hoc tests to identify intergroup differences are provided in [Table A.1](#).

Details regarding the DLCN score criteria in patients with premature MI are presented in [Table A.2](#). Of the 29 patients with premature MI and “probable” or “definite” FH, 14 (48%) underwent molecular diagnosis and eight (57%) were found to have mutations (87.5% in the low-density lipoprotein receptor and 12.5% in apolipoprotein B). Angiographic characteristics of patients with premature MI according to FH diagnosis are provided in [Table 2](#). Patients with “probable” or “definite” FH had significantly higher rates of multivessel disease (48% vs 23% in patients with no FH;  $P = 0.01$ ). Rate of revascularization by stent was significantly higher in patients with suspected FH ( $P = 0.04$ ).

### **Control population: CARVAR 92 cohort**

Of the 32,721 subjects of the CARVAR 92 prospective cohort, 9900 aged  $\leq 50$  years were identified (mean age,  $44.5 \pm 4.0$  years; male sex, 57.7%). Clinical data are presented in [Table 3](#). According to the DLCN score, 9343 subjects (94.4%, 95% CI 93.9–94.8%) had no FH, 541 (5.5%, 95% CI 5.0–5.9%) had “possible” FH and 16 (0.16%, 95% CI 0.09–0.26%) had “probable” or “definite” FH. LDL-C was significantly higher in subjects with “probable” or “definite” FH than in patients without FH ( $265 \pm 52$  vs  $127 \pm 31$  mg/dL;  $P < 0.0001$ ).

### **Comparison between cohorts**

Clinical characteristics in both populations are compared in [Table 4](#). Male sex, current smoking, diabetes mellitus and dyslipidaemia were more frequent in patients with premature MI. [Fig. 2](#) presents the FH prevalence in both cohorts (patients with premature MI and subjects from the CARVAR 92 cohort). Prevalence of “possible” FH and of “probable” or “definite” FH was significantly higher in the group of patients with premature MI in comparison with the control population ( $P < 0.001$  in both cases). Conversely, prevalence of patients with no FH was higher in the control population ( $P < 0.001$ ). Considering patients with “probable” or “definite” FH, FH prevalence was 39 times greater in patients with premature MI than in the control population ( $P < 0.0001$ ). [Table 5](#) shows cardiovascular risk factors associated with premature MI after adjustment in the multivariable model. FH (“probable” or “definite”) was the strongest risk factor for premature acute MI (OR 38.4, 95% CI 19.1–79.4) ([Central illustration](#)).

## Discussion

In the present study, we evaluated FH prevalence in two different cohorts of young patients (aged  $\leq 50$  years). FH prevalence was  $> 30$ -fold higher in young patients with premature MI than in the general population of the same age, from the same population pool. Indeed, subjects participating in the CARVAR 92 study live in the Hauts de Seine department, as do patients with premature MI referred to Ambroise Paré University Hospital, which receives 90% of the MI cases from the Hauts de Seine department. This equates to 1 in 16 people presenting with premature MI versus 1 in 500 people in the general population. Previous studies found that the prevalence of FH was about 5 to 10 times higher among patients hospitalized for ACS compared with the general population, without taking into consideration the actual population [13, 27]. To our knowledge, this is the first study comparing the prevalence of FH in young patients with premature MI and in the general population.

FH prevalence in patients who experience premature ACS is uncertain. Danchin et al. reported a prevalence of 8% for FH assessed by DLCN score in a cohort of 846 patients aged  $< 50$  years with premature MI [28]. In a study of 1451 patients with premature ACS (before the age of 55 years for men and 60 years for women), Nanchen et al. found an FH prevalence of 4.8%, using the DLCN score [15]. In our study, the prevalence of “probable” or “definite” FH reached 6% in the group of patients with premature MI. The lower prevalence in the Swiss register reported by Nanchen et al. may be explained by an older age. Prevalence of FH depends on age: the younger the patients, the higher the prevalence. The prevalence of FH in the general population aged  $< 50$  years included in the large CARVAR 92 cohort is an estimated 0.16%, which is consistent with previous studies [1, 6].

A notable finding of our study is the high prevalence of FH in young patients with MI compared with the general population. This encourages clinicians to screen patients with premature MI for FH at the time of MI hospitalization. Patients should benefit from intensive lipid-lowering therapy and close follow-up [29-34]. In our study, patients with “probable” or “definite” FH had more severe coronary artery disease, with a higher rate of multivessel disease, as shown in previous studies [16, 28]. The long-term risks of death or major cardiovascular events are known to be higher in patients with FH than in those without FH, even in patients who receive high-intensity statins or combined statin/ezetimibe therapy [28, 35]. This population of young patients, however, should benefit from more potent lipid-lowering therapy, such as PCSK9 inhibitors. Moreover, relatives should be screened

to enable early initiation of optimal treatment (diet, statin, smoking cessation). In the present study, we observed a high proportion of patients with a family history of coronary artery disease who smoked (92 smokers out of 125 patients; 74%, 95% CI 65–81%); they represent a potential target for primary prevention screening to get them to quit smoking before a first atherothrombotic event. Furthermore, the prevalence of diabetes mellitus was high in the premature MI cohort (9%), as shown previously in the literature [36, 37]. Associated metabolic syndrome, obesity and insulin resistance are powerful factors for the development of premature coronary artery disease.

Systematic screening for FH in the general population is also of interest, as the first clinical manifestation of FH is often premature ACS. However, this remains a real challenge [38, 39], and is one of the purposes of our large CARVAR 92 study cohort. Patients with “possible”, “probable” or “definite” FH were offered non-invasive cardiovascular tests at our university hospital, high-intensity lipid-lowering therapy when appropriate and an interview with a nutritionist and a smoking cessation specialist. For this purpose, the use of a simple validated clinical and biochemical score is convenient for assessment of FH diagnosis and is feasible in daily practice.

## **Study limitations**

Our study has several limitations. First, although the CARVAR 92 cohort is a prospective cohort, patients with premature myocardial infarction were included retrospectively from our database. Thus, not all data concerning family history of hypercholesterolaemia, xanthomata or arcus cornealis were available for the calculation of the complete DLCN score. However, previous FH studies [15, 28] have assessed FH using a simplified DLCN score, which we used. Furthermore, the prevalence of these criteria is low, and has little effect on the interpretation of FH, as demonstrated by these previous studies [17, 21]. Second, we did not systematically perform genetic molecular analysis to identify mutations associated with FH. However, in most studies, the frequency of detectable mutations in patients with clinically “definite” or “probable” FH is between 60% and 80% [39, 40]. This suggests that a considerable proportion of patients with FH have either a polygenic cause of the disease or that other genes, yet to be identified, are involved. Finally, many confounding factors (such as socioeconomic status) were not assessed in the present study, which may have influenced the final multivariable analysis.

## **Conclusions**

FH is > 30-fold more common in patients referred for premature MI than in the general population of the same age, from the same population pool; it is also a predominant and independent associated factor for acute MI before the age of 50 years. This highlights the need for FH screening after a first episode of MI to intensify lipid-lowering therapy and enable early identification of family members.

## **Acknowledgements**

We kindly thank the municipalities and medical teams from our partner cities Antony, Asnières-sur-Seine, Bagneux, Châtenay-Malabry, Colombes, Fontenay-aux-Roses, Gennevilliers, Issy-les-Moulineaux, Le Plessis-Robinson, Montrouge, Nanterre, Foch Hospital in Suresnes, Neuilly-Courbevoie Hospital and Marie-Thérèse Health Centre in Malakoff, and all physicians involved in the screening campaign.

We thank the Caisse Primaire d'Assurance Maladie of the Hauts de Seine, Christian Collard its general director, his predecessor Alain Bourez, and the board members President Patric Mourgère and President Aurélie Le Galoudec.

## **Sources of funding**

The authors received no financial support for the research, authorship and/or publication of this article.

## **Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

## References

- [1] Akioyamen LE, Genest J, Shan SD, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *BMJ Open* 2017;7:e016461.
- [2] Berard E, Bongard V, Haas B, et al. Prevalence and Treatment of Familial Hypercholesterolemia in France. *Can J Cardiol* 2019;35:744-52.
- [3] Bucholz EM, Rodday AM, Kolor K, Khoury MJ, de Ferranti SD. Prevalence and Predictors of Cholesterol Screening, Awareness, and Statin Treatment Among US Adults With Familial Hypercholesterolemia or Other Forms of Severe Dyslipidemia (1999-2014). *Circulation* 2018;137:2218-30.
- [4] de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation* 2016;133:1067-72.
- [5] Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Circulation* 2020;141:1742-59.
- [6] Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;34:3478-90a.
- [7] Ferrieres J, Bruckert E, Beliard S, et al. [Familial hypercholesterolemia: A largely underestimated cardiovascular risk]. *Ann Cardiol Angeiol (Paris)* 2018;67:1-8.
- [8] Seguro F, Rabes JP, Taraszkievicz D, Ruidavets JB, Bongard V, Ferrieres J. Genetic diagnosis of familial hypercholesterolemia is associated with a premature and high coronary heart disease risk. *Clin Cardiol* 2018;41:385-91.
- [9] Beliard S, Rabes JP, Cariou B, et al. [Familial hypercholesterolemia: An under-diagnosed and under-treated disease. Survey of 495 physicians]. *Presse Med* 2018;47:e159-e67.
- [10] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88.

- [11] Amor-Salamanca A, Castillo S, Gonzalez-Vioque E, et al. Genetically Confirmed Familial Hypercholesterolemia in Patients With Acute Coronary Syndrome. *J Am Coll Cardiol* 2017;70:1732-40.
- [12] Benedek P, Eriksson M, Duvefelt K, et al. Genetic testing for familial hypercholesterolemia among survivors of acute coronary syndrome. *J Intern Med* 2018;284:674-84.
- [13] Gencer B, Nanchen D. Identifying familial hypercholesterolemia in acute coronary syndrome. *Curr Opin Lipidol* 2016;27:375-81.
- [14] Kramer AI, Trinder M, Brunham LR. Estimating the Prevalence of Familial Hypercholesterolemia in Acute Coronary Syndrome: A Systematic Review and Meta-analysis. *Can J Cardiol* 2019;35:1322-31.
- [15] Nanchen D, Gencer B, Auer R, et al. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. *Eur Heart J* 2015;36:2438-45.
- [16] Rerup SA, Bang LE, Mogensen UM, et al. The prevalence and prognostic importance of possible familial hypercholesterolemia in patients with myocardial infarction. *Am Heart J* 2016;181:35-42.
- [17] Singh A, Gupta A, Collins BL, et al. Familial Hypercholesterolemia Among Young Adults With Myocardial Infarction. *J Am Coll Cardiol* 2019;73:2439-50.
- [18] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol* 2018;72:2231-64.
- [19] Hauguel-Moreau M, Pepin M, Hergault H, et al. Long-term changes of the cardiovascular risk factors and risk scores in a large urban population. *Eur J Prev Cardiol* 2021.
- [20] Karam C, Beauchet A, Czernichow S, et al. Trends in Cardiovascular Disease Risk Factor Prevalence and Estimated 10-Year Cardiovascular Risk Scores in a Large Untreated French Urban Population: The CARVAR 92 Study. *PLoS One* 2015;10:e0124817.
- [21] Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab* 2012;97:3956-64.
- [22] Dorsch MF, Lawrance RA, Durham NP, Hall AS. Familial hypercholesterolaemia is underdiagnosed after AMI. *BMJ* 2001;322:111.

- [23] Genest JJ, Jr., Martin-Munley SS, McNamara JR, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. *Circulation* 1992;85:2025-33.
- [24] Besseling J, Kindt I, Hof M, Kastelein JJ, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis* 2014;233:219-23.
- [25] Ruel I, Aljenedil S, Sadri I, et al. Imputation of Baseline LDL Cholesterol Concentration in Patients with Familial Hypercholesterolemia on Statins or Ezetimibe. *Clin Chem* 2018;64:355-62.
- [26] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.
- [27] Harada-Shiba M, Ako J, Arai H, et al. Prevalence of familial hypercholesterolemia in patients with acute coronary syndrome in Japan: Results of the EXPLORE-J study. *Atherosclerosis* 2018;277:362-8.
- [28] Danchin N, Farnier M, Zeller M, et al. Long-term outcomes after acute myocardial infarction in patients with familial hypercholesterolemia: The French registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction program. *J Clin Lipidol* 2020;14:352-60 e6.
- [29] Landmesser U, Chapman MJ, Farnier M, et al. European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. *Eur Heart J* 2017;38:2245-55.
- [30] Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J* 2008;29:2625-33.
- [31] Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. *Circulation* 2011;124:2202-7.
- [32] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;376:1713-22.



- [33] Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018;379:2097-107.
- [34] Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *BMJ* 2008;337:a2423.
- [35] Seguro F, Bongard V, Berard E, Taraszkievicz D, Ruidavets JB, Ferrieres J. Dutch Lipid Clinic Network low-density lipoprotein cholesterol criteria are associated with long-term mortality in the general population. *Arch Cardiovasc Dis* 2015;108:511-8.
- [36] Collet JP, Zeitouni M, Procopi N, et al. Long-Term Evolution of Premature Coronary Artery Disease. *J Am Coll Cardiol* 2019;74:1868-78.
- [37] Zeitouni M, Clare RM, Chiswell K, et al. Risk Factor Burden and Long-Term Prognosis of Patients With Premature Coronary Artery Disease. *J Am Heart Assoc* 2020;9:e017712.
- [38] Defesche JC. Defining the challenges of FH screening for familial hypercholesterolemia. *J Clin Lipidol* 2010;4:338-41.
- [39] Rabes JP, Beliard S, Carrie A. Familial hypercholesterolemia: experience from France. *Curr Opin Lipidol* 2018;29:65-71.
- [40] Civeira F, Ros E, Jarauta E, et al. Comparison of genetic versus clinical diagnosis in familial hypercholesterolemia. *Am J Cardiol* 2008;102:1187-93, 93 e1.

## Figure legends

**Figure 1.** Study flow chart. DLCN: Dutch Lipid Clinic Network; FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction.

**Figure 2.** Prevalence of familial hypercholesterolaemia (FH) in patients with premature myocardial infarction (MI) ( $n = 457$ ) and in the general control population (CARVAR 92 cohort) ( $n = 9900$ ).

<sup>a</sup>  $P < 0.001$ . [Publisher: \* to be changed to <sup>a</sup> in figure.]

**Central illustration.** Prevalence of familial hypercholesterolaemia (FH) among young adults with myocardial infarction (MI) ( $n = 457$ ) and in the general control population (CARVAR 92 cohort) ( $n = 9900$ ), and cardiovascular risk factors associated with premature acute MI.

**Table 1** Baseline characteristics in patients with premature myocardial infarction.

	All patients ( <i>n</i> = 457)	DLCN score			<i>P</i>
		No FH ( <i>n</i> = 220; 48%)	Possible FH ( <i>n</i> = 208; 46%)	Probable or definite FH ( <i>n</i> = 29; 6%)	
Age (years)	44.7 ± 5.5	44.6 ± 5.5	45.0 ± 5.2	44.0 ± 5.8	0.6
Male sex	391 (86)	180 (82)	184 (88)	27 (93)	0.08
Family history	125 (27)	0 (0)	110 (54)	15 (52)	< 0.001
Current smoking	329 (72)	157 (71)	155 (75)	17 (59)	0.2
Hypertension	86 (19)	40 (18)	40 (19)	6 (21)	0.9
Diabetes mellitus	39 (9)	13 (6)	24 (12)	2 (7)	0.1
Body mass index (kg/m <sup>2</sup> )	26.8 ± 4.7	26.7 ± 4.2	26.6 ± 4.4	28.5 ± 5.2	0.6
History of stroke	2 (0.4)	0 (0)	2 (1)	0 (0)	0.3
History of PAD	2 (0.4)	0 (0)	2 (1)	0 (0)	0.3
Lipid measures					
Total cholesterol (mg/dL)	228 ± 94	190 ± 37	238 ± 72	438 ± 21	< 0.001
LDL-C (mg/dL)	142 ± 53	116 ± 26	152 ± 39	273 ± 73	< 0.001
HDL-c (mg/dL)	45 ± 36	43 ± 18	48 ± 49	47 ± 17	0.3
Triglycerides (mg/dL)	152 ± 71	152 ± 73	156 ± 72	132 ± 42	0.3
Medication at admission					
Antiplatelet therapy	29 (6)	6 (3)	18 (9)	5 (17)	0.002
Lipid-lowering therapy	41 (9)	7 (3)	24 (12)	10 (34)	< 0.001
Anticoagulant treatment	4 (0.9)	1 (0.5)	3 (1)	0 (0)	0.5
Diagnosis					
OHCA	31 (7)	19 (9)	12 (6)	0 (0)	0.07
STEMI	300 (66)	140 (64)	141 (68)	19 (66)	0.9
NSTEMI	126 (28)	61 (28)	55 (26)	10 (34)	0.8
Medication at discharge					
Statins	437 (96)	206 (94)	203 (98)	28 (97)	0.1

High-dose statins <sup>a</sup>	301 (66)	146 (66)	136 (65)	19 (66)	0.9
Ezetimibe	9 (2)	3 (1)	1 (1)	5 (17)	< 0.001
Dual antiplatelet therapy	421 (92)	198 (90)	194 (93)	29 (100)	0.99
Antihypertensives	448 (98)	214 (97)	206 (99)	28 (97)	0.99

Data are expressed as mean  $\pm$  standard deviation or number (%). Cardiovascular risk factor definitions are given in [Appendix](#). DLCN: Dutch Lipid Clinic Network; FH: familial hypercholesterolaemia; HDL-c: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NSTEMI: non-ST-segment elevation myocardial infarction; OHCA: out-of-hospital cardiac arrest; PAD: peripheral artery disease; STEMI: ST-segment elevation myocardial infarction.

<sup>a</sup> High-dose statins were defined as: atorvastatin 80 mg/day, simvastatin 80 mg/day, pravastatin 40 mg/day or rosuvastatin 20 mg/day.

**Table 2** Procedural characteristics in patients with premature myocardial infarction according to familial hypercholesterolaemia diagnosis.

	All patients ( <i>n</i> = 457)	Simplified DLCN score			<i>P</i>
		No FH (< 3 points) ( <i>n</i> = 220; 48%)	Possible FH (3–5 points) ( <i>n</i> = 208; 46%)	Probable or definite FH (> 5 points) ( <i>n</i> = 29; 6%)	
Number of affected vessels <sup>a</sup>					
1	301 (66)	155 (70)	131 (63)	15 (52)	0.07
2	104 (23)	42 (19)	50 (24)	12 (41)	0.02
3	32 (7)	8 (4)	22 (11)	2 (7)	0.01
≥ 2	136 (30)	50 (23)	72 (35)	14 (48)	0.01
Non-obstructive CAD	20 (4)	15 (6)	5 (3)	0 (0)	0.5
Revascularization					
Stent	382 (84)	174 (79)	183 (88)	25 (86)	0.04
Balloon only	10 (2)	6 (3)	3 (1)	1 (3)	0.4
CABG	7 (2)	1 (1)	6 (2)	0 (0)	0.1
Medical treatment only	58 (13)	39 (17)	16 (9)	3 (11)	0.006
Pre PCI TIMI flow 0	263 (58)	131 (60)	118 (58)	14 (48)	0.5
Post PCI TIMI flow 0	19 (4)	12 (5)	6 (3)	1 (3)	0.4

Data are expressed as number (%). CABG: coronary artery bypass graft; CAD: coronary artery disease; DLCN: Dutch Lipid Clinic Network; FH: familial hypercholesterolaemia; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction risk score.

<sup>a</sup> Number of affected vessels was defined as the number of major coronary vessels (≥ 2 mm in diameter) with > 70% stenosis of the diameter.

**Table 3** Clinical characteristics in the control population (CARVAR 92 cohort).

	All subjects ( <i>n</i> = 9900)	Simplified DLCN score		
		No FH (< 3 points) ( <i>n</i> = 9343; 94.4%)	Possible FH (3–5 points) ( <i>n</i> = 541; 5.5%)	Probable or definite FH (> 5 points) ( <i>n</i> = 16; 0.2%)
Age (years)	44.5 ± 4.0	44.5 ± 4.0	45.3 ± 3.8	45.2 ± 4.0
Male sex	5717 (58)	5360 (57)	347 (64)	10 (63)
Family history	2906 (29)	2615 (28)	276 (51)	15 (94)
Current smoking	2507 (25)	2331(25)	172 (32)	4 (25)
Hypertension	1857 (19)	1649 (18)	203 (38)	5 (31)
Diabetes mellitus	210 (2)	174 (2)	36 (7)	0 (0)
Body mass index (kg/m <sup>2</sup> )	25.6 ± 4.4	25.5 ± 4.4	26.9 ± 4.8	25.9 ± 3.9
Lipid measures				
Total cholesterol (mg/dL)	208 ± 38	205 ± 34	256 ± 54	331 ± 81
LDL-C (mg/dL)	130 ± 35	127 ± 31	180 ± 50	265 ± 52
HDL-c (mg/dL)	56 ± 16	56 ± 16	52 ± 14	53 ± 17
Triglycerides (mg/dL)	109 ± 68	107 ± 65	145 ± 100	210 ± 120

Data are expressed as mean ± standard deviation or number (%). DLCN: Dutch Lipid Clinic Network; FH: familial hypercholesterolaemia; HDL-c: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

**Table 4** Clinical characteristics in both populations (patients with premature myocardial infarction and subjects from the CARVAR 92 cohort).

	Patients with premature MI ( <i>n</i> = 457)	Subjects from the CARVAR 92 cohort ( <i>n</i> = 9900)	<i>P</i>
Age (years)	44.7 ± 5.5	44.5 ± 4.0	0.32
Male sex	391 (86)	5717 (58)	< 0.001
Family history	125 (27)	2906 (29)	0.36
Current smoking	329 (72)	2507 (25)	< 0.001
Hypertension	86 (19)	1857 (19)	0.97
Diabetes mellitus	39 (9)	210 (2)	< 0.001
Body mass index (kg/m <sup>2</sup> )	26.8 ± 4.7	25.6 ± 4.4	0.41
Lipid measures			
Total cholesterol (mg/dL)	228 ± 94	208 ± 38	< 0.001
LDL-C (mg/dL)	142 ± 53	130 ± 35	< 0.01
HDL-c (mg/dL)	45 ± 36	56 ± 16	< 0.001
Triglycerides (mg/dL)	152 ± 71	109 ± 68	< 0.001

Data are expressed as mean ± standard deviation or number (%). HDL-c: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction..

**Table 5** Cardiovascular risk factors associated with premature myocardial infarction after adjustment in the multivariable model.

Cardiovascular risk factors	Patients with premature MI ( <i>n</i> = 457)	Patients without premature MI ( <i>n</i> = 9900)	Adjusted OR (95% CI) <sup>a</sup>	<i>P</i>
FH	29 (6.3)	16 (0.2)	38.4 (19.1–79.4)	< 0.0001
Sex (male)	391 (86)	5717 (58)	3.2 (2.4–4.2)	< 0.0001
Current smoking	329 (72)	2507 (25)	6.9 (5.6–8.6)	< 0.0001
Diabetes mellitus	39 (9)	210 (2)	2.7 (1.8–3.9)	< 0.0001
Family history	125 (27)	2906 (29)	0.9 (0.7–1.1)	0.35
High blood pressure	86 (19)	1857 (19)	0.85 (0.7–1.1)	0.23

Data are expressed as number (%). CI: confidence interval; FH: familial hypercholesterolaemia; MI: myocardial infarction; OR: odds ratio.

<sup>a</sup> ORs and their 95% CIs were estimated directly from a logistic regression model.



### Patients with premature MI

Screening : 465 patients

Exclusion : 8 patients  
(LDL-c missing data)

457 included patients

### CARVAR 92 cohort

Screening : 32,721 patients

Exclusion : 22,821 patients  
(Age > 50)

9,900 included patients

**Assessment of FH prevalence according to DLCN score**

*MI : myocardial infarction, LDL : low-density lipoprotein, FH : familial hypercholesterolemia, DLCN : dutch lipid clinic network*

Probable  
or definite FH

6.4

0.2\*

Premature MI cohort (<50)

CARVAR 92 cohort

Possible FH

45.5

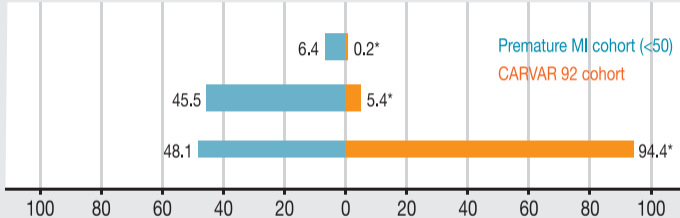
5.4\*

No FH

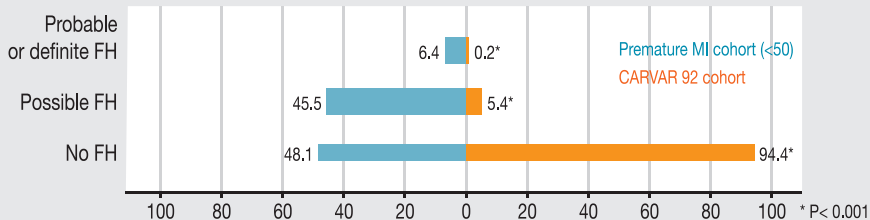
48.1

94.4\*

\*  $P < 0.001$ , FH = familial hypercholesterolemia, MI = myocardial infarction



## Prevalence of familial hypercholesterolemia (FH) among young adults with myocardial infarction (MI) (n = 457) and from control population (CARVAR 92 cohort, n = 9,900)



## Cardiovascular risk factors associated with premature acute MI

