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CLINICAL RESEARCH

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

Prévalence de l'hypercholestérolémie familiale chez les patients présentant un syndrome coronaire aigu prématuré

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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.

☆ Tweet: in a study including 457 pts with premature myocardial infarction (MI) and 9900 healthy subjects (< 50 yo), 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).

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

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.

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

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.

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 $\geq$ 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 Online material), 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 Online materialTable A.1.

Details regarding the DLCN score criteria in patients with premature MI are presented in Online materialTable 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 ≤ 50 years were identified (mean age, 44.5 ± 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 ± 52 vs. 127 ± 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 ≤ 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

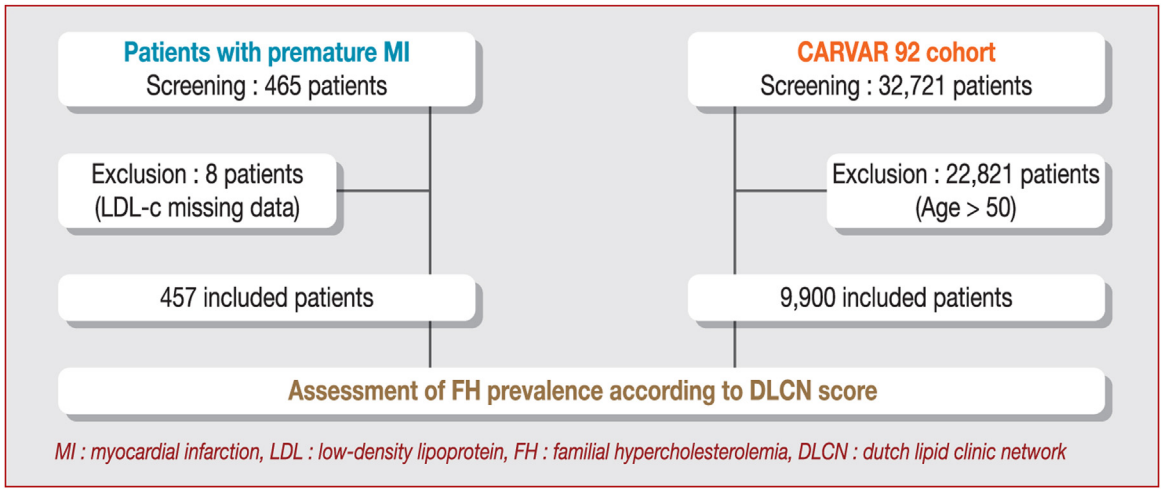

Figure 1. Study flow chart. DLCN: Dutch Lipid Clinic Network; FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction.

Table 1 Baseline characteristics in patients with premature myocardial infarction.

	All patients	DLCN score			*P*
		No FH	Possible FH	Probable or definite FH	
	(*n* = 457)	(*n* = 220; 48%)	(*n* = 208; 46%)	(*n* = 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^2)	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[a]	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

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. Data are expressed as mean ± standard deviation or number (%). Cardiovascular risk factor definitions are given in Appendix.

[a] 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	Simplified DLCN score			*P*
		No FH (< 3 points)	Possible FH (3—5 points)	Probable or definite FH (> 5 points)	
	(*n* = 457)	(*n* = 220; 48%)	(*n* = 208; 46%)	(*n* = 29; 6%)	
Number of affected vessels[a]					
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

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. Data are expressed as number (%).
[a] 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	Simplified DLCN score		
		No FH (< 3 points)	Possible FH (3—5 points)	Probable or definite FH (> 5 points)
	(*n* = 9900)	(*n* = 9343; 94.4%)	(*n* = 541; 5.5%)	(*n* = 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^2)	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

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

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

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

	Patients with premature MI ($n = 457$)	Subjects from the CARVAR 92 cohort ($n = 9900$)	*P*
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^2)	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

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

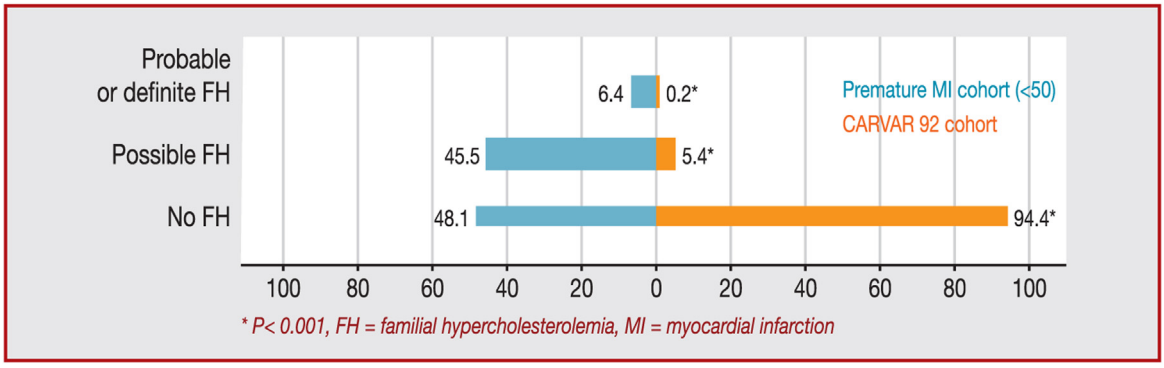

Figure 2. Prevalence of familial hypercholesterolaemia (FH) in patients with premature myocardial infarction (MI) ($n = 457$) and in the general control population (CARVAR 92 cohort) ($n = 9900$). [a]: $P < 0.001$.
Central illustration. Prevalence of familial hypercholesterolaemia (FH) among young adults 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 5 Cardiovascular risk factors associated with premature myocardial infarction after adjustment in the multivariable model.

Cardiovascular risk factors	Patients with premature MI ($n = 457$)	Patients without premature MI ($n = 9900$)	Adjusted OR (95% CI)[a]	*P*
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

CI: confidence interval; FH: familial hypercholesterolaemia; MI: myocardial infarction; OR: odds ratio. Data are expressed as number (%).
[a] ORs and their 95% CIs were estimated directly from a logistic regression model.

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.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2021.11.005.

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