Original Article

Effects of Familial Hypercholesterolemia on Major Adverse Cardiac and Cerebrovascular Events in Patients with Premature Coronary Artery Disease: A Retrospective Cohort Study

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Highlights

- Probable FH (LDL-C ≥190 mg/dL) was identified in 20.2% of PCAD patients.
- Probable FH linked to higher all-cause mortality ($p < 0.05$) but not MACCE incidence.
- Early mortality in FH may mask MACCE risk, warranting aggressive lipid management.

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ABSTRACT

Background: Evaluating the impact of familial hypercholesterolemia (FH) on the occurrence of major adverse cardiac and cerebrovascular events (MACCE) in patients with premature coronary artery disease.

Methods: This retrospective cohort study was conducted at Tehran Heart Center, between 2004 and 2011. 3907 patients with acute coronary syndrome (ACS) who underwent coronary angiography were collected from registry systems. The patients were divided into "Unlikely FH" and "Probable FH" using a modified and simplified version of the Dutch Lipid Clinic Network (DLCN) criteria. After a 10-year follow-up, different components of MACCE between the two groups were evaluated.

Results: Data from 3206 premature coronary artery disease patients with baseline LDL values were extracted. 2558 (79.8%) patients were categorized into the Unlikely FH group, and 648 (20.2%) patients were in the probable FH group. In the unlikely FH group, 745 (29.1%) patients experienced at least one of the MACCE events. In the probable FH group, 193 (29.7%) experienced at least one MACCE event. The difference between groups did not reach the level of significance ($p>0.05$). The mortality rate in the unlikely FH group was 6.9% (n=179), while in the probable FH group, the mortality rate was 7.8% (n=51) ($p<0.05$).

Conclusions: In the present study, patients with probable FH pose a higher risk regarding mortality than unlikely FH patients.

Keywords: Familial Hypercholesterolemia; MACCE; Premature Coronary Artery Disease; Acute Coronary Syndrome

Introduction

Familial hypercholesterolemia (FH) is an inherited disorder of cholesterol metabolism.[1,2] This condition accelerates atherosclerosis and increases the risk of premature cardiovascular disease.[2-5] Based on the Dutch Lipid Clinic Network (DLCN) criteria, approximately 10% of patients diagnosed with premature coronary artery disease (CAD) in hospitals are classified as having possible or definite FH.[6]

The prevalence of heterozygous FH ranges from 1 in 250 to 1 in 500, while homozygous FH occurs in 1 in 160,000 to 1 in 100,000 individuals.[2,7,8] Given FH's high prevalence and its role in premature cardiovascular disease, early screening, diagnosis, and treatment are critical.[8] Studies indicate that untreated heterozygous FH leads to CAD in 30% of men by age 50 and 50% of women by age 60.[3] Moreover, nearly all untreated homozygous FH patients develop cardiovascular disease before age 30.[7]

Of 200 World Health Organization (WHO) member countries, only 22 have reported accurate data on FH prevalence.[8] In Asian countries, studies estimate that only 1% of patients with FH are diagnosed.[9] Unfortunately, owing to inadequate screening programs, most cases are identified only after the first acute coronary syndrome (ACS).[8]

Numerous studies demonstrate that the timely detection and proper management of FH can significantly reduce the incidence of ACS and other cardiovascular diseases.[1,3,8,10] Nonetheless, few researchers have examined how FH affects long-term prognosis in these patients. This issue is critical, as it would highlight the importance of FH evaluation after cardiovascular events to guide targeted therapy.[11]

In this study, we aimed to investigate the prevalence, demographic characteristics, and prognostic significance of FH among patients with premature CAD.

Methods

Study population

The current retrospective cohort study was conducted on 3,907 individuals with premature CAD. Data were extracted from the Tehran Heart Center-Premature Coronary Atherosclerosis Cohort (THC-PAC) project,[12] including patients enrolled between 2011 and 2019, with each followed for at least 2 years until 2021. Follow-up was conducted via telephone every 6 months and clinical visits annually.

Premature CAD was defined as ACS with >50% stenosis in coronary vessels in men aged <45 and women aged <55. Demographic data (age, sex, and body mass index) and cardiovascular risk factors (hypertension, diabetes, and smoking) were collected. Past medical history, family history, and medication use (particularly lipid-lowering drugs) were also recorded.

This study was conducted following the tenets of the Helsinki Declaration. The study protocol received approval from the institutional review board Tehran University of Medical Science (Approval ID: IR.TUMS.MEDICINE.REC.1398.769), and all patient information was carefully verified while ensuring patient confidentiality and satisfaction.

For FH diagnosis, patients were categorized into "unlikely FH" and "probable FH" groups using a modified and simplified version of the DLCN criteria.[13] The diagnostic criteria incorporated two key parameters: baseline plasma low-density lipoprotein-cholesterol (LDL-C) levels and age at premature CAD onset. According to the modified DLCN criteria, premature CAD was assigned 2 points, LDL-C ≥190 mg/dL received 3 points, and LDL-C <155 mg/dL was given 0 points. Probable FH was defined as a total score of ≥5 points, while unlikely FH was classified as <3 points. Due to unavailable data, parameters including tendon xanthomas and genetic mutations were not considered in the scoring system.

Previous studies have demonstrated that moderate-dose statin therapy typically reduces LDL-C levels by 30–50%.[14-16] To account for this pharmacological effect in our analysis, we adjusted the LDL-C values of statin-treated patients by multiplying their admission levels by a correction factor of 1.43.

Risk factors

We conducted comprehensive assessments of cardiovascular risk factors present before or during hospitalization. Diabetes mellitus was defined as hemoglobin A1c >6.5%, fasting blood glucose >126 mg/dL, or current use of glucose-lowering medications. Hypertension was diagnosed based on either: (1) two documented measurements of systolic blood pressure ≥140 mm Hg, (2) two measurements of diastolic blood pressure ≥90 mm Hg, or (3) active antihypertensive treatment. Central obesity was classified as body mass index ≥30 kg/m². Smoking status was categorized as current, former, or never smoker. A positive family history of premature CAD requires diagnosis in first-degree male relatives <55 years or female relatives <65 years. Left ventricular systolic dysfunction was defined as ejection fraction ≤35% on pre-discharge echocardiography performed before discharge.

Medications and lab data

All discharge medications were systematically documented, including antiplatelet agents (aspirin and clopidogrel), renin-angiotensin system inhibitors (ACE inhibitors or ARBs), beta-blockers, and statins. These pharmacologic interventions were prescribed in accordance with the current American College of Cardiology/American Heart Association (ACC/AHA) clinical practice guidelines. In addition, we recorded baseline serum laboratory values, including triglyceride (TG) levels, high-density lipoprotein cholesterol (HDL-C), and creatinine (CR) for all study participants.

Follow-up and objectives

Within the THC-PAC project, patients underwent annual follow-up through clinical visits or telephone contact. This study had three primary aims: first, to establish the prevalence of FH among patients with premature CAD; second, to examine the association between FH and major adverse cardiac and cerebrovascular events (MACCE) in this population; and third, to evaluate the impact of FH on individual MACCE components. These components consisted of nonfatal myocardial infarction, cerebrovascular events, revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft surgery), hospital readmission for ACS, and all-cause mortality.

Statistical Analysis

Continuous variables were assessed for distribution using histograms, measures of central tendency, and dispersion. Normally distributed parameters (age, body mass index, and HDL-C) were expressed as mean±standard deviation (SD) and compared between probable and unlikely FH groups using independent samples t-tests. Non-normally distributed variables (serum TG and Cr) were analyzed using the Mann-Whitney U test. Categorical variables were presented as frequencies (percentages) and compared via chi-square tests between the groups.

Both unadjusted and adjusted associations of FH with MACCE and all-cause mortality were evaluated using Cox proportional hazards models, reporting hazard ratios (HRs) with 95% confidence intervals (CIs). For analysis of individual MACCE components, competing risk regression models were employed to calculate subdistribution hazard ratios (sHR) with corresponding 95% CIs. Variables demonstrating univariate associations ($P<0.1$) were included as potential confounders in adjusted models. All analyses were conducted using SPSS (version 24.0; IBM Corp.) and Stata (release 14.2; StataCorp. LP) statistical software packages.

Results

Following exclusions for missing baseline LDL values or loss to follow-up, our final cohort was composed of 3,206 patients (Figure 1). The study population had a mean age of 45.66±5.94 years, with 1,724 females (53.8%) and 1,482 males (46.2%).

Regarding lipid-lowering therapy prior to admission, 1,083 patients (33.8%) were treatment-naïve, while 2,123 patients (66.2%) reported using at least one lipid-lowering agent. Based on LDL-C stratification, 2,558 patients (79.8%) with levels <155 mg/dL were classified as unlikely FH, whereas 648 patients (20.2%) with LDL-C≥190 mg/dL comprised the probable FH group. Complete

demographic characteristics, medication profiles, and cardiovascular risk factors for both groups are presented in (Table 1).

The incidence of MACCE was comparable between the groups, occurring in 745 patients (29.1%) in the unlikely FH group and 193 patients (29.7%) in the probable FH group (P>0.05). When analyzing MACCE components excluding all-cause mortality (ACS, cerebrovascular accident, and revascularization), only ACS occurrence showed a nonsignificant trend toward higher frequencies in the probable FH group (8.4% vs. 8.1% in the unlikely FH group; P>0.05). The influence of additional risk factors, pharmacotherapy, and laboratory parameters on MACCE incidence is detailed in (Table 2).

All-cause mortality rates differed significantly between the groups, occurring in 51 patients (7.8%) in the probable FH cohort and 179 patients (6.9%) in the unlikely FH cohort (P<0.05). The association between mortality and various risk factors, medications, and laboratory parameters is presented in (Table 3).

Cox regression analysis revealed progressively increasing cumulative hazards for both MACCE and mortality over time. While no significant intergroup difference emerged in MACCE cumulative hazards (P>0.05) (Figure 2A-B), the probable FH group demonstrated significantly greater cumulative mortality hazard (P<0.05) (Figure 2C-D).

The mean time to first MACCE occurrence was significantly shorter in the probable FH group (74.0±40.0 months) than in the unlikely FH group (79.5±42.8 months; P<0.05). Concerning the initial MACCE presentation, death occurred as the first event in 40 patients (6.1%) with probable FH compared with 143 patients (5.5%) with unlikely FH, demonstrating a statistically significant difference after adjustment (P<0.05).

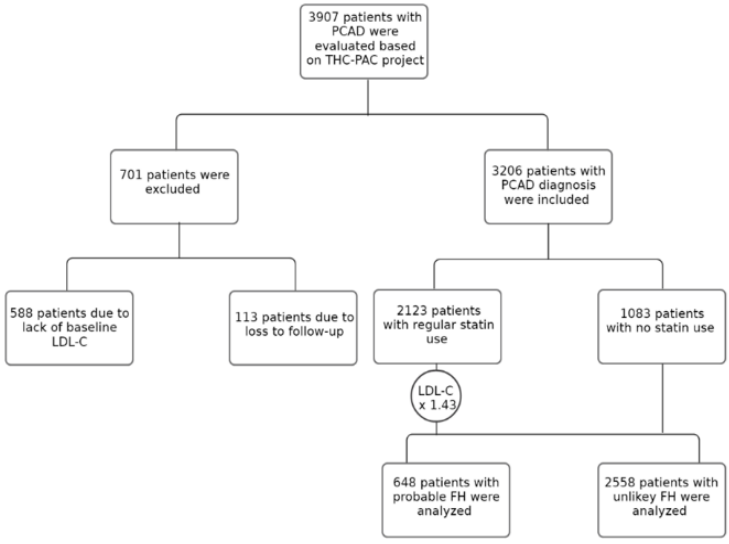
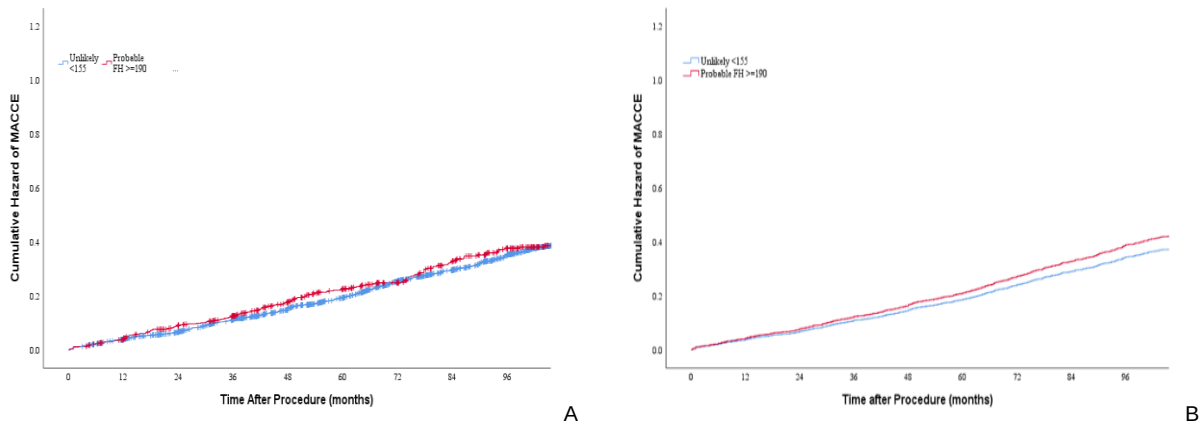


Figure-1: The image presents the study flowchart of patients with premature coronary artery disease included in the analysis.



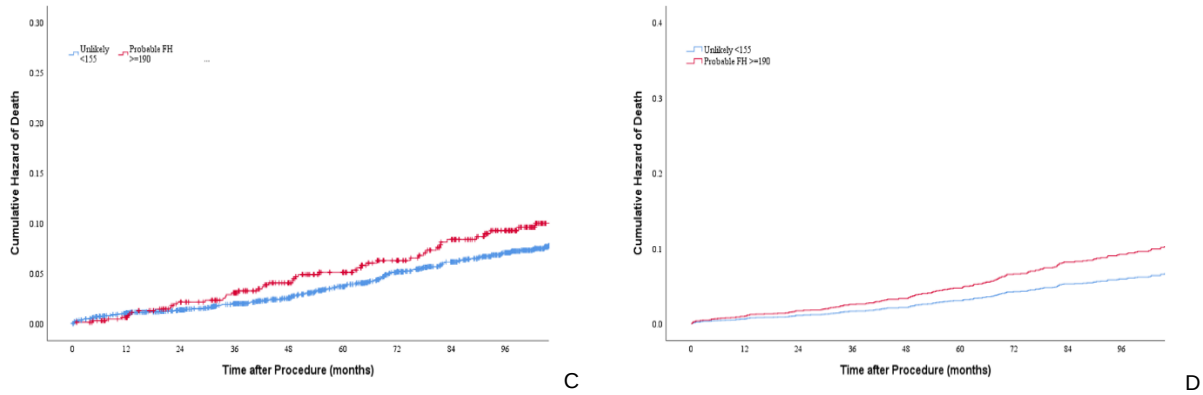


Figure-2: Cumulative hazards of (A) unadjusted and (B) adjusted MACCE, and (C) unadjusted and (D) adjusted mortality over time (months). Significant differences were observed in mortality curves (C and D; P <0.05). Adjusted models were controlled for diabetes, high-density lipoprotein cholesterol, triglycerides, creatinine, and use of aspirin, beta-blockers, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, and clopidogrel.

Table 1. Demographic features and clinical characteristics of the patients in the two groups of unlikely and probable familial hypercholesterolemia

	Unlikely FH (LDL<155) Total=2558	Probable FH (LDL≥190) (Total=648)	P-value
Sex, n (%) Female	1372 (53.6%)	352 (54.3%)	0.755
Male	1186 (46.4%)	296 (45.7%)	
Age (years), mean ± SD	45.68 ± 5.8	45.60 ± 6.1	0.783
Positive family History, n (%)	1213 (47.4%)	295 (45.6%)	0.401
Diabetes, n (%)	975 (38.1%)	220 (34%)	0.052
Hypertension, n (%)	1274 (49.8%)	324 (50%)	0.943
Current smoker, n (%)	630 (24.6%)	169 (26.1%)	0.436
Obesity, n (%)	943 (37%)	227 (35.2%)	0.423
EF<35 %, n (%)	162 (6.6%)	39 (6.2%)	0.679
Aspirin, n (%)	1934 (82.4%)	549 (85.5%)	0.065
ACE or ARB, n (%)	1373 (58.6%)	422 (65.7%)	0.001
B-blocker, n (%)	1954 (83.5%)	556 (86.6%)	0.057
Clopidogrel, n (%)	588 (25.1%)	208 (32.4%)	<0.001

Abbreviations: FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein-cholesterol; EF, ejection fraction; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Table 2. The effect of cardiac and cerebrovascular risk factors, medications, and lab data of patients with premature coronary artery disease on the on the occurrence of MACE

MACE occurrence	Hazard Ratio	P-value	95% CI for Hazard Ratio	
			Lower	Upper
Probable FH	1.129	0.153	0.956	1.332
Diabetes	1.367	<0.001	1.192	1.569
Aspirin usage	1.172	0.128	0.955	1.438
ACE or ARB usage	1.179	0.025	1.021	1.361
B-blocker usage	0.803	0.017	0.671	0.962
Clopidogrel	0.924	0.319	0.790	1.080
Triglyceride	1.001	0.016	1.000	1.001
HDL	1.000	0.941	0.994	1.007
Creatinine	1.165	<0.001	1.091	1.243

Abbreviations: MACE, major adverse cardiovascular events; FH, familial hypercholesterolemia, ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; HDL, high-density lipoprotein.

Table 3. The effect of cardiovascular risk factors, medications, and lab data of patients with premature coronary artery disease on the all-cause mortality.

All-cause Mortality	Hazard Ratio	P-value	95% CI for Hazard Ratio	
			Lower	Upper
Probable FH	1.548	0.009	1.115	2.150
Diabetes	2.133	<0.001	1.618	2.810
Aspirin usage	1.133	0.543	0.757	1.695
ACE or ARB usage	1.519	0.006	1.128	2.045
B-blocker usage	0.587	0.002	0.422	0.816
Clopidogrel	0.679	0.026	0.484	0.954
Triglyceride	1.000	0.566	0.998	1.001
HDL	0.971	<0.001	0.957	0.986
Creatinine	1.377	<0.001	1.277	1.486

Abbreviations: FH, familial hypercholesterolemia, ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; HDL, high-density lipoprotein.

Discussion

Our study evaluated 3,206 patients with premature CAD, classifying them by LDL-C thresholds: probable FH (LDL-C≥190 mg/dL) and unlikely FH (LDL-C<155 mg/dL). This stratification revealed a probable FH prevalence of 20.2%, contrasting with 79.8% in the unlikely FH group. Our findings align partially with international data: an Indian study (2016–2018) reported a 15% prevalence rate of probable/definite FH,[17] whereas a Danish study (1998-2012) documented a lower prevalence rate (9.7%).[18] This discrepancy likely reflects our inclusion of high-probability cases in the probable FH category, unlike the more stringent classifications in previous studies.

The reported prevalence of FH in our cohort (20.2% probable FH) differs from other international studies. A Swiss investigation (2009–2013) identified lower rates of probable/definite FH (5.5%), alongside higher possible FH prevalence (18.2%).[11] Similarly, a 2018 Gulf region study reported 3.7% probable/definite FH and 28% possible FH prevalence.[19] These discrepancies primarily reflect methodological differences in FH classification. Our modified DLCN criteria incorporated only two variables—premature CAD and baseline LDL-C levels—as data regarding tendon xanthomas, genetic mutations, and family history were unavailable for comprehensive scoring.

During follow-up, patients with probable FH demonstrated a nonsignificantly elevated risk of composite MACCE (excluding mortality) compared with unlikely FH patients (HR:1.12). When examining individual MACCE components, only ACS showed a numerically higher incidence in the probable FH group, although this difference similarly failed to constitute statistical significance (P>0.05).

Our findings are in line with Danish cohort data (1998–2012) showing nonsignificantly elevated ACS recurrence risk in probable FH patients during follow-up.[18] Nevertheless, the Swiss study (2009–2013) reported more pronounced differences, with probable FH patients demonstrating double the CAD recurrence risk within the first year post-discharge despite intensive statin therapy.[11] While we similarly observed increased ACS recurrence in probable FH patients, the magnitude of risk was substantially lower than reported in the Swiss cohort. This discrepancy may reflect methodological differences: (1) our longer follow-up duration (mean 74–79 months vs. 1-year assessment) and (2) variation in follow-up protocols (our combined telephone/clinical visits versus exclusive clinical monitoring in the Swiss study).

A Japanese study (2009–2017) reported a higher MACCE occurrence rate in probable/definite FH patients than in unlikely FH patients during a 40-month follow-up, although the difference was nonsignificant, consistent with our findings. In our study, probable FH patients experienced first MACCE events significantly earlier than unlikely FH patients. Additionally, death as the first MACCE occurred more frequently in the probable FH group than in the unlikely FH group.

Conclusion

In the present study, the incidence of MACCE did not differ significantly between unlikely FH and probable FH groups, while all-cause mortality showed significant differences. The similar MACCE rates between the groups may reflect earlier mortality in probable FH patients, potentially limiting the time for other MACCE components to develop.

Declarations:
Ethical Approval

the Ethics Committee of Tehran University of Medical Science (Approval ID: IR.TUMS.MEDICINE.REC.1398.769)

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Conflict of Interest

The authors report no conflict of interest.

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