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Familial Hypercholesterolemia Among Young Adults With Myocardial Infarction

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ABSTRACT

BACKGROUND There are limited data on the prevalence and treatment of familial hypercholesterolemia (FH) among U.S. adults who experience a myocardial infarction (MI) at a young age.

OBJECTIVES This study aimed to evaluate the prevalence of clinically defined FH and examine the rates of statin utilization and low-density lipoprotein cholesterol (LDL-C) achieved 1-year post MI.

METHODS The YOUNG-MI registry is a retrospective cohort study that includes patients who experience an MI at or below age 50 years between 2000 and 2016 at 2 academic centers. Probable or definite FH was defined by the Dutch Lipid Clinic criteria. Outcomes included the proportion of patients classified as probable or definite FH, use of lipid-lowering therapy, and LDL-C achieved 1-year post MI.

RESULTS The cohort consisted of 1,996 adults with a median age of 45 years; 19% were women, and 54% had ST-segment elevation MI. Probable/definite FH was present in 180 (9%) of whom 42.8% were not on statins prior to their MI. Of the 1,966 patients surviving until hospital discharge, 89.4% of FH patients and 89.9% of non-FH patients were discharged on statin therapy ($p = 0.82$). Among FH patients, 63.3% were discharged on high-intensity statin compared with 48.4% for non-FH patients ($p < 0.001$). At 1-year follow-up, the percent reduction in LDL-C among FH patients was −44.4% compared with −34.5% ($p = 0.006$) in non-FH patients. The proportion of patients with LDL-C ≥70 mg/dl was higher among FH patients (82.2%) compared with non-FH patients (64.5%; $p < 0.001$).

CONCLUSIONS Clinically defined FH was present in nearly 1 of 10 patients with MI at a young age. Only two-thirds of FH patients were discharged on high-intensity statin therapy, and the vast majority had elevated LDL-C at 1 year. These findings reinforce the need for more aggressive lipid-lowering therapy in young FH and non-FH patients post-MI.
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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

ASCVD = atherosclerotic cardiovascular disease

CAD = coronary artery disease

CI = confidence interval

DLC = Dutch Lipid Clinic

FH = familial hypercholesterolemia

HR = hazard ratio

LDL-C = low-density lipoprotein cholesterol

MI = myocardial infarction

PCSK9 = proprotein convertase subtilisin/kexin type 9

Familial hypercholesterolemia (FH) is a common, yet under-recognized condition that leads to premature cardiovascular disease and increased cardiovascular morbidity and mortality (1). However, despite advances in diagnostics and screening, FH remains undiagnosed in >90% of patients (2). While the prevalence of FH among the U.S. general population ranges from approximately 1 in 212 to 1 in 250 (3,4), there are limited data regarding prevalence of FH among patients who experience a cardiovascular event at a young age.

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Statin therapy reduces cardiovascular events in patients with elevated cholesterol (5), but recent data suggest that young adults, including those with low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dl, have low rates of statin use, with less than one-half of such patients receiving a statin despite their high risk of atherosclerotic events from an early age (6). Similarly, recent data from the nationally representative NHANES (National Health and Nutrition Examination Survey) suggest that young patients with FH may be undertreated, with only 13% of young patients with FH receiving any lipid-lowering therapy (3). This pattern of clinical management runs counter to the new 2018 guideline on the management of blood cholesterol, which recognizes severe hypercholesterolemia (LDL-C ≥190 mg/dl) as a group at very high risk of future events and recommends initiation of maximally tolerated statin therapy without additional risk calculations (7).

Given this context, the objectives of this study were: 1) to evaluate the proportion of patients that met standard clinical criteria for FH among a cohort of patients that experienced a myocardial infarction (MI) at a young age; 2) to evaluate the frequency and intensity of lipid-lowering therapy, as well as the LDL-C achieved 1-year post MI; and 3) to compare differences in long-term, all-cause, and cardiovascular mortality among patients with and without FH.

METHODS

STUDY POPULATION. The design of the YOUNG-MI registry has been previously described (8). This is a retrospective cohort study from 2 large academic medical centers (Brigham and Women's Hospital and Massachusetts General Hospital) that included patients who were admitted with an MI at or before 50 years of age between 2000 and 2016. The presence and type of MI were adjudicated using the Third Universal Definition of MI (9). For the present analysis, only patients with type 1 MI were included. Individuals with known coronary artery disease (CAD) (defined as prior MI or revascularization) or missing LDL-C were excluded.

IDENTIFICATION OF PATIENTS WITH FH. The Dutch Lipid Clinic (DLC) Network criteria (2) was used to identify patients with FH. This is a contemporary definition that has been widely used in most U.S. and

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European cohorts (3,4,10). The DLC criteria scores points based on personal or family history of premature coronary or vascular disease, findings of arcus cornealis or tendon xanthomas on clinical examination, pre-treatment LDL-C levels, and presence of functional mutations in the *LDLR*, *apoB,* or proprotein convertase subtilisin/kexin type 9 (*PCSK9)* genes. According to these criteria (Online Table 1), probable FH was assigned for patients with 6 to 8 points, whereas definite FH was assigned for patients with >8 points. For the purposes of this analysis, and as has been done in most studies, patients classified as probable or definite FH were considered to have clinically defined FH (3,4,10).

Whereas the DLC criteria uses an age cutoff of <60 years to define family history of premature CAD for first-degree female relatives, we used an age cutoff of <65 years to conform to the definition used in the YOUNG-MI registry, similar to the one currently used in guidelines (7) and other studies (11).

A text search algorithm was used to identify patients with the following keywords (and their variations) in their medical record: "xanthoma," "arcus," "familial hypercholesterolemia," and "xanthelasma"; the records of these patients were further adjudicated by study physicians, and points for the DLC criteria were awarded wherever appropriate. Among patients on lipid-lowering therapy at baseline, we estimated untreated LDL-C levels by multiplying the on-treatment LDL with a correction factor based on the type and dose of therapy, as done in other studies (10).

RISK FACTORS. A detailed review of the electronic medical record was conducted to determine the presence of cardiovascular risk factors during or before the index admission. Diabetes was defined as fasting plasma glucose >126 mg/dl, hemoglobin A1c ≥6.5% or diagnosis/treatment for diabetes. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or diagnosis or treatment of hypertension. Obesity was defined as a body mass index ≥30 kg/m^2, or a diagnosis of obesity. Smoking was defined as current (tobacco products used within the last month), former, or never. The atherosclerotic cardiovascular disease (ASCVD) 10-year risk score was calculated based on data available prior to MI or at time of presentation using the pooled cohort equations, as previously described (12). Lipoprotein(a) testing results were available in a subset of patients. Over time, 2 different assays with different reference ranges were used. Therefore, we analyzed lipoprotein(a) as a binary variable indicating whether it was above or below the upper limit of normal for the specific reference range used at that time.

MEDICATIONS. A detailed review of electronic medical records was used to determine the prescription of guideline-directed medical therapy at the time of hospital discharge. Patients who died in-hospital were excluded from this specific analysis; but not from other analyses. Medications captured included aspirin, $P2Y_{12}$ inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. In addition, use of lipid-lowering therapy such as statins, ezetimibe, niacin, fibrates, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors was also captured. Intensity of statin therapy was defined as described in the 2013 American College of Cardiology (ACC)/American Heart Association cholesterol guidelines (13).

OUTCOMES. The pre-specified outcomes of interest were: 1) the proportion of patients with probable or definite FH; 2) the proportion of patients discharged on any statin therapy and on high-intensity statin therapy; 3) the reduction in LDL-C achieved at 1-year follow-up; and 4) survival free from all-cause death and cardiovascular death. For LDL-C reduction, we specifically evaluated the proportion of patients at 1 year with LDL-C ≥70 mg/dl, LDL-C ≥100 mg/dl, and ≥50% reduction in LDL-C, as these have been identified as subgroups for whom additional therapies such as ezetimibe and PCSK9 inhibitors may be considered per the 2018 guidelines on the management of blood cholesterol (7).

Vital status was assessed with linkage with the Partners Healthcare electronic medical record system, the Social Security Administration's Death Master File, and the National Death Index, and was censored on the date of the latest query. The cause of death was adjudicated by 2 independent cardiologists using electronic health records, records from the Massachusetts Department of Vital Statistics, and death certificates obtained from the National Death Index. In cases of disagreement, consensus for the cause of death was reached by the adjudication committee. The cause of death was categorized into cardiovascular death, noncardiovascular death, or undetermined cause of death. If the cause of death was undetermined, deaths were categorized as non-cardiovascular death. The definition of cardiovascular death was adapted from the 2014 ACC definition for cardiovascular endpoint events (14) and was previously detailed in the study design publication (8).

DATA MANAGEMENT. Study-related data for all patients who meet inclusion criteria were stored on a customized secure electronic adjudication system and REDCap. REDCap is an encrypted, secure, Health Insurance Portability and Accountability

TABLE 1 Baseline Characteristics

	Unlikely/Possible FH (n = 1,816, 91%)	Probable/Definite FH (n = 180, 9%)	p Value
Demographics			
Age at event, yrs	45.0 (42.0–48.0)	45.5 (40.5–48.0)	0.92
Women	344 (18.9)	38 (21.1)	0.49
Race			
White	1,338 (73.7)	129 (71.7)	0.11
Black	129 (7.1)	14 (7.8)	
Hispanic or Latino	123 (6.8)	20 (11.1)	
Asian	67 (3.7)	3 (1.7)	
Missing/other	159 (8.8)	14 (7.8)	
Risk factors			
ST-segment elevation MI	993 (54.7)	88 (48.9)	0.16
Diabetes	350 (19.5)	42 (23.6)	0.20
Hypertension	827 (46.0)	103 (57.9)	0.003
Obesity	527 (33.8)	60 (39.0)	0.21
Current Smoking	933 (51.9)	95 (53.4)	0.75
Family history of premature CAD	465 (25.6)	129 (71.7)	<0.001
ASCVD risk score	4.6 (2.6–7.5)	6.5 (4.0–11.6)	<0.001
Medical therapy on admission			
Statin therapy	188 (10.4)	103 (57.2)	<0.001
Ezetimibe	6 (0.3)	2 (1.1)	0.16
Aspirin	176 (9.7)	44 (24.4)	<0.001
Beta-blockers	180 (9.9)	39 (21.7)	<0.001
ACE inhibitor/ARB	179 (9.9)	30 (16.7)	0.007
Biomarkers on admission			
Creatinine, mg/dl	1.0 ± 0.4	1.0 ± 0.4	0.99
Normalized troponin (x ULN assay)*	42.1 (10.6–152.2)	37.0 (9.0–112.2)	0.13
Total cholesterol, mg/dl	185.8 ± 46.9	259.1 ± 92.4	<0.001
LDL-C, mg/dl	113.2 ± 35.4	179.8 ± 87.5	<0.001
Triglycerides, mg/dl	147 (102–215)	169 (111–268)	0.006
HDL-C, mg/dl	36.9 ± 10.3	36.8 ± 9.7	0.95
Elevated lipoprotein(a), n (%)†	42 (38.5)	11 (55.0)	0.169

Values are median (interquartile range), n (%), or mean ± SD. *Normalized to times upper limit of normal for assay. †Elevated above upper limit of normal for assay. Available for 129 patients.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction.

Act-compliant web platform for electronic data capture and serves as an intuitive interface to enter data with real time validation (15). The YOUNG-MI registry has been approved by the Institutional Review Board at Partners HealthCare.

STATISTICAL ANALYSIS. Categorical variables were reported as frequencies and proportions and compared with the chi-square or Fisher exact test. Continuous variables were reported as medians or means and compared with Student's *t*-tests or the Mann-Whitney *U* test. All analyses were performed using Stata version 14.2 (StataCorp, College Station, Texas). Cox proportional hazards models were constructed for survival free from all-cause and cardiovascular death. Proportional hazards assumption was assessed by analyzing the Schoenfeld residuals. Multivariable risk adjustment was performed using variables that had significant univariate association or are known to be associated with either all-cause or cardiovascular death. The unimputed LDL-C at baseline was used as reference to calculate change at 1 year. Waterfall plots of reduction in LDL-C at 1 year follow-up were generated using Tableau Desktop version 10.5 (Tableau Software, Seattle, Washington).

We also performed a sensitivity analysis using other criteria used to define FH, including a modification of the DLC criteria that has been used in other cohorts, which does not consider physical examination or genetic testing (3,10), the Simon Broome criteria (16,17), and criteria proposed by the ACC (13) and American Heart Association (18). To determine the yield of screening for FH using the DLC criteria, and to allow for comparison with other studies (19), we evaluated the prevalence of FH among different subgroups in our cohort, including those who have LDL-C ≥160 mg/dl, a family history of premature CAD, and both of the above conditions.

RESULTS

The cohort consisted of 1,996 adults with a median age of 45 years (interquartile range: 42 to 48 years) who experienced a type I MI. Among this cohort, 382 (19.1%) were women and 1,081 (54.2%) had an ST-segment elevation MI. The likelihood of FH based on the DLC was as follows: unlikely FH (n = 1,067; 53.5%), possible FH (749; 37.5%), probable FH (128; 6.4%) and definite FH (52; 2.6%). Therefore, a total of 180 patients (9%; 95% confidence interval [CI]: 7.8% to 10.4%), met criteria for clinically defined FH.

BASELINE CHARACTERISTICS. Table 1 depicts differences in baseline characteristics among patients with and without FH. Physical examination findings among patients with FH are provided in Online Table 2. Notably, age did not differ significantly between patients with and without FH. Patients with FH had significantly higher rates of hypertension (57.9% vs. 46%; p = 0.003), family history of premature CAD (71.7% vs. 25.6%; p < 0.001), and a significantly higher 10-year ASCVD risk score (median 6.5 vs. 4.6; p < 0.001). Overall, statin use prior to MI was low, and most patients (n = 1,705; 85.4%) were not on any lipid-lowering therapy prior to their MI. Even among patients with FH, 77 (42.8%) were not on any statin therapy prior to their MI, suggesting that they were unaware or not treated for their underlying condition. The above baseline characteristics stratified by the 4 categories of increasing likelihood of FH are provided in Online Table 3.

MEDICAL THERAPY AT DISCHARGE. When examining medical therapy for patients who survived until discharge (n = 1,966), 1,768 (89.9%) patients were prescribed statin therapy, but of these only 978 (55.3%) were prescribed a high-intensity agent. When comparing statin utilization between admission and discharge, utilization of any statin therapy and high-intensity statin therapy increased for both FH and non-FH patients (Online Figure 1). Patients with FH were significantly more likely to be discharged on a high-intensity statin (63.3% vs. 48.4%; p < 0.001), discharged on ezetimibe (5% vs. 1%; p < 0.001), and participate in cardiac rehabilitation (24.4% vs. 16.6%; p = 0.013) compared with those without FH (**Table 2**). A PCSK9 inhibitor was prescribed at discharge in 1 patient in the non-FH group.

LDL-C AT 1 YEAR POST-MI. Of the 1,966 patients who survived until discharge, LDL-C achieved at 1 year was available in 650. Among these patients, those with FH had a significantly higher median LDL-C at 1 year (96 mg/dl vs. 80 mg/dl; p < 0.001) despite a significantly higher absolute (−77 mg/dl vs. −39 mg/dl; p < 0.001) and percent (−44.4% vs. −34.5%; p = 0.006) reduction in LDL-C compared with non-FH patients (**Table 3**). At 1 year, the proportion of FH patients with LDL-C ≥70 and ≥100 mg/dl was significantly higher compared with those without FH (82.2% vs. 64.5% and 43% vs. 25.2%, respectively; p < 0.001 for both). Among FH patients, 44 (42.7%) had a 50% or greater reduction in LDL-C compared with 130 (25.1%) of non-FH patients (p < 0.001). **Figure 1** shows a waterfall plot of the percent reduction in LDL-C among patients with and without FH, stratified by whether the LDL-C at 1 year was <70 or ≥70 mg/dl. Even though there was a significant reduction in LDL-C for FH and non-FH patients, those with FH were more likely to have LDL-C ≥70 mg/dl, as depicted in red in **Figure 1**. These findings were similar when restricting only to patients discharged on high-intensity statins and are provided in Online Table 4.

TRENDS IN STATIN USE. Although there was no change in the proportion of patients discharged on statin therapy during the 16-year study period, there was significantly higher high-intensity statin use (Online Figure 2A) for both FH and non-FH patients over time. Correspondingly, over the same period there was a significant increase in the magnitude of LDL-C reduction at 1 year compared with baseline (Online Figure 2B).

LONG-TERM FOLLOW-UP. Over a median follow-up of 11.2 years (interquartile range: 7.3 to 14.2 years), 228 (11.4%) deaths were observed, of which 104 were adjudicated to be from a cardiovascular cause. All-cause mortality was not significantly different among those with and without FH (log-rank p = 0.85) (**Figure 2A**). In Cox proportional hazards modeling for survival free from all-cause death, the unadjusted hazard ratio (HR) for FH was 1.05 (95% CI: 0.65 to 1.68), which decreased to 1.00 (95% CI: 0.61 to 1.64; p = 0.90) in a multivariable model that included demographics, cardiovascular risk factors and comorbidities, and in-hospital treatment and medications at discharge (**Table 4**). Similarly, cardiovascular death was not significantly different among those with and

TABLE 2 Management and Therapy at Discharge (N = 1,966)

	No FH (n = 1,786, 91%)	FH (n = 180, 9%)	p Value
Revascularization			
Cardiac catheterization	1,717 (96.6)	168 (96.0)	0.66
Coronary revascularization	1,561 (86.0)	151 (83.9)	0.43
Coronary artery bypass grafting	128 (7.0)	18 (10.0)	0.17
Medical therapy at hospital discharge			
Any statin	1,607 (90.0)	161 (89.4)	0.80
Statin intensity*			
No statin	179 (10.0)	19 (10.6)	<0.001
Low-intensity/unknown dose	64 (3.6)	4 (2.2)	
Moderate-intensity	679 (38.0)	43 (23.9)	
High-intensity	864 (48.4)	114 (63.3)	
Ezetimibe	17 (1.0)	9 (5.0)	<0.001
Niacin	34 (1.9)	1 (0.6)	0.37
Fibrates	54 (3.0)	5 (2.8)	1.00
Aspirin	1,699 (95.1)	170 (94.4)	0.72
Beta-blockers	1,640 (91.8)	162 (90.0)	0.40
$P2Y_{12}$ inhibitors	1,490 (83.4)	143 (79.4)	0.18
ACE inhibitor/ARB	1,134 (63.5)	99 (55.0)	0.029
Diuretics	179 (10.0)	24 (13.3)	0.16
Cardiac rehabilitation	302 (16.6)	44 (24.4)	0.013

Values are n (%). *Based on 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults.
Abbreviations as in Table 1.

TABLE 3 LDL-C Achieved at 1-Year Follow-Up (N = 650)

	No FH (n = 543, 84%)	FH (n = 107, 16%)	p Value
LDL-C at 1 yr	80.0 (60.0 to 101.0)	96.0 (75.0 to 123.0)	<0.001
Change in LDL-C at 1 yr, mg/dl*	−39.0 (−69.0 to −11.0)	−77.0 (−127.0 to −14.0)	<0.001
Percent change in LDL-C at 1 yr*	−34.5 (−50.0 to −10.2)	−44.4 (−62.0 to −9.7)	0.006
Proportion with LDL-C at 1 yr ≥70 mg/dl	350 (64.5)	88 (82.2)	<0.001
Proportion with LDL-C at 1 yr ≥100 mg/dl	137 (25.2)	46 (43.0)	<0.001
Proportion with ≥50% reduction in LDL-C at 1 yr*	130 (25.1)	44 (42.7)	<0.001

Values are median (interquartile range) or n (%). *Unimputed LDL-C at baseline was used to calculate change.
Abbreviations as in Table 1.

FIGURE 1 Waterfall plot of %LDL-C Reduction at 1 Year Among Young Adults With MI Stratified by Presence or Absence of FH

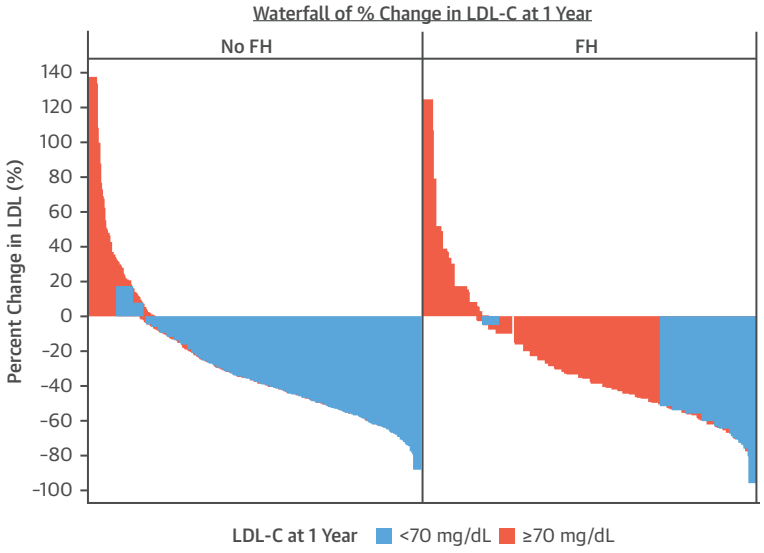


Figure shows the waterfall of percent low-density lipoprotein cholesterol (LDL-C) reduction at 1 year among patients without familial hypercholesterolemia (FH) **(left)** and patients with FH **(right)**. **Blue** represents LDL-C at 1 year <70 mg/dl. **Red** represents LDL-C at 1 year ≥70 mg/dl. FH patients had significantly higher proportion of patients with LDL-C at 1 year ≥70 mg/dl **(red)**.

without FH (log-rank p value = 0.65) (Figure 2B). In Cox proportional hazards modeling survival free from cardiovascular death, the unadjusted HR for FH was 0.84 (95% CI: 0.39 to 1.81), which increased to 0.88 (95% CI: 0.40 to 1.92; p = 0.75) in a multivariable model that included demographics, cardiovascular risk factors and comorbidities, and in-hospital treatment and medications at discharge (Table 4).

PREVALENCE IN SUBGROUPS AND BASED ON OTHER DIAGNOSTIC CRITERIA. Among patients with a family history of premature CAD in a first-degree relative (n = 594), 129 (21.7%) met criteria for probable/definite FH. Among 481 patients with LDL-C ≥160 mg/dl, 171 (35.6%) met criteria for probable/definite FH, and among patients who had both history of premature CAD and LDL ≥160 mg/dl (n = 193), 124 (64.3%) met criteria for probable/definite FH (Central Illustration). Prevalence of FH based on other diagnostic criteria for FH is presented in Online Table 5.

DISCUSSION

In this study, the largest to examine the prevalence and treatment of FH in young adults with MI, we found the proportion of clinically-defined FH to be 9%, or nearly 1 in 10. Over 40% of the FH patients were not on statin therapy prior to MI, suggesting they were unaware, undiagnosed, untreated, or nonadherent to recommended therapy due to adverse effects or personal preferences. At the time of discharge, 10% of FH patients were not prescribed statins, whereas only two-thirds were prescribed a high-intensity statin. Despite a large reduction in LDL-C at 1 year, the vast majority of FH patients still had an LDL-C ≥70 mg/dl, and nearly one-half had LDL-C ≥100 mg/dl. Over long-term follow-up, no significant differences in all-cause mortality or cardiovascular mortality were observed in FH patients compared with non-FH patients.

PREVALENCE OF FH IN THE GENERAL POPULATION. Our finding that clinically defined FH was present in nearly 1 in 10 patients with premature CAD is nearly 20× higher than that observed in the general U.S. population (see Online Table 6 for a summary of studies examining the prevalence of FH across various cohorts [20]). In the United States, de Ferranti et al. (4) evaluated the prevalence of FH in NHANES from 1999 to 2012 and found it to be present in 1 in 250 (0.4%) U.S. adults. In a more recent analysis, Bucholz et al. (3) evaluated the prevalence of FH in NHANES from 1999 to 2014 and found it to be present in 1 in 212 (0.47%), thus affecting nearly 1

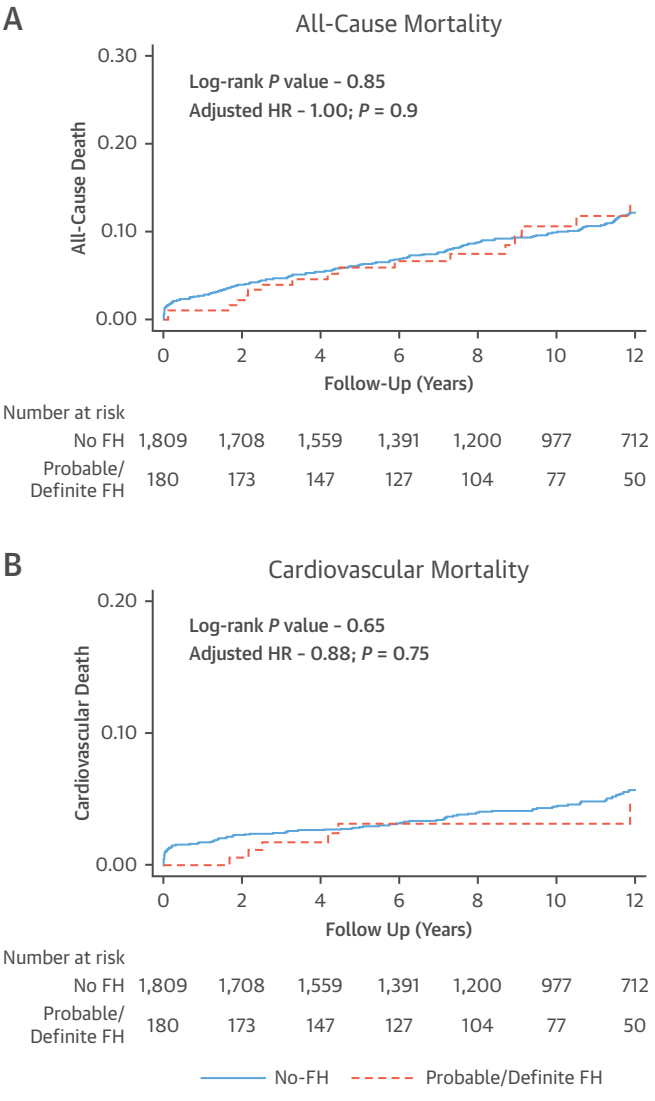
million U.S. adults (3). Given that both studies lacked confirmatory genetic testing and did not include physical examination findings suggestive of FH, the true prevalence of definite/probable FH could have been underestimated.

PREVALENCE OF FH AMONG PATIENTS WITH ACUTE CORONARY SYNDROME. Nanchen at al. (10) evaluated the prevalence of FH in a multicenter study in Switzerland—SPUM-ACS (Special Program University Medicine-Acute Coronary Syndrome)—using criteria similar to that used in our study. Among nearly 4,800 patients with acute coronary syndrome (ACS), they found the prevalence of FH to be 1.6%. However, when limited to patients with premature ACS (defined as men age ≤55 years, and women age ≤60 years) the FH prevalence increased to 4.8% (10). In an analysis from the EUROASPIRE (European Action on Secondary and Primary Prevention through Intervention to Reduce Events) IV survey, which included 7,000 patients hospitalized for ACS or revascularization procedure, the prevalence of FH was estimated at 8.3%, which increased to 15.4% when restricted to the 2,212 patients age <60 years (11). Other smaller studies have also estimated the prevalence of FH in different countries (21). Pang et al. (22) found FH prevalence to be 14.3% among 175 patients age <60 years admitted to a CCU in Australia, while Al-Rasadi et al. (23) reported an FH prevalence of 3.7% in a cohort of 3,224 patients with ACS from the Arabian Gulf. The wide variations in the reported estimate in these studies may be related to variability in the true prevalence of FH across distinct, potentially genetically diverse populations (24), the age of the cohort studied, and the criteria used to define FH (25).

UNDERUTILIZATION OF STATINS AND OTHER LIPID-LOWERING THERAPIES. In our study, there was significant underutilization of statins for FH patients prior to the admission for MI (57%). Similar undertreatment trends have also been observed by other groups. For example, in the NHANES study, Bucholz et al. (3) reported that among FH patients, only 15% were taking high-intensity statins despite high rates of screening and awareness. Those authors also highlighted that young adults (defined as age <40 years) are at high risk of undertreatment (3). While the above estimates are based on data from the general population, even when examining post-ACS patients, high-intensity statin use among FH patients remains low (21). The exact drivers of this underutilization of statin therapy in younger FH patients remains unresolved but requires further investigation given the omission of potentially life-saving interventions. The impact on the loss of future life years saved and lost productivity is even more apparent in younger MI patients with FH.

In our study, although 89% of the cohort was discharged on a statin, only 63% of patients with FH were discharged on a high-intensity statin, and despite a nearly 50% reduction in LDL-C, the vast

FIGURE 2 All-Cause and Cardiovascular Mortality Among Young Adults With MI Stratified by Presence or Absence of FH



(A) Kaplan-Meier failure curves for all-cause death. **(B)** Kaplan-Meier failure curves for cardiovascular death. No significant difference was observed between patients with and without familial hypercholesterolemia (FH) in unadjusted or adjusted models for both outcomes. HR = hazard ratio.

TABLE 4 Long-Term Outcomes

	All-Cause Mortality			Cardiovascular Mortality		
	No FH (n = 1,816, 91%)	FH (n = 180, 9%)	p Value	No FH (n = 1,816, 91%)	FH (n = 180, 9%)	p Value
Crude mortality	209 (11.5)	19 (10.6)	0.81	97 (5.3)	7 (3.9)	0.48
Annualized event rate	1.12 (0.98–1.29)	1.18 (0.76–1.86)	0.78	0.51 (0.42–0.63)	0.48 (0.21–0.92)	0.70
Unadjusted HR	Ref.	1.05 (0.65–1.68)	0.85	Ref.	0.84 (0.39–1.81)	0.65
Adjusted HR*	Ref.	1.00 (0.61–1.64)	0.9	Ref.	0.88 (0.40–1.92)	0.75

Values are n (%) or hazard ratio (HR) (95% confidence interval). *Adjusted for age, sex, cardiovascular risk factors, Charlson comorbidity index, revascularization status, medications at discharge, and participation in cardiac rehabilitation.

FH = familial hypercholesterolemia.

majority had elevated LDL-C at 1 year. Specifically, 43% of FH patients had an LDL-C ≥100 mg/dl, and 82% FH patients had an LDL-C ≥70 mg/dl. In comparison, in the Swiss SPUM-ACS cohort, approximately 70% were discharged on a high-intensity statin; nonetheless, 63% had an LDL-C ≥100 mg/dl while 95% had an LDL-C ≥70 mg/dl (10).

The use of nonstatin lipid-lowering therapy was trivial in our study and represents a missed opportunity, because such agents further reduce LDL levels and cardiovascular events (26,27). The use of ezetimibe, which is often well tolerated, was very low in this FH cohort and also in recent PCSK9 inhibitor trials. Of note, in the recently completed ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, the benefit of adding a PCSK9 inhibitor to statin therapy was especially apparent among those with LDL levels >100 mg/dl, which is directly relevant to those patients identified here (28,29). The 2018 guideline on the management of blood cholesterol (7) recommends considering ezetimibe or a PCSK9 inhibitor for high-risk patients with ASCVD and LDL-C 70 mg/dl or higher who are on maximally tolerated statin therapy, or maximally tolerated lipid-lowering therapy, respectively. Because all patients with a recent ACS are considered high-risk, the vast majority of both FH and non-FH patients in our cohort may be eligible for such therapies, with the threshold for additional therapies in FH patients being lower (LDL-C 100 mg/dl or higher).

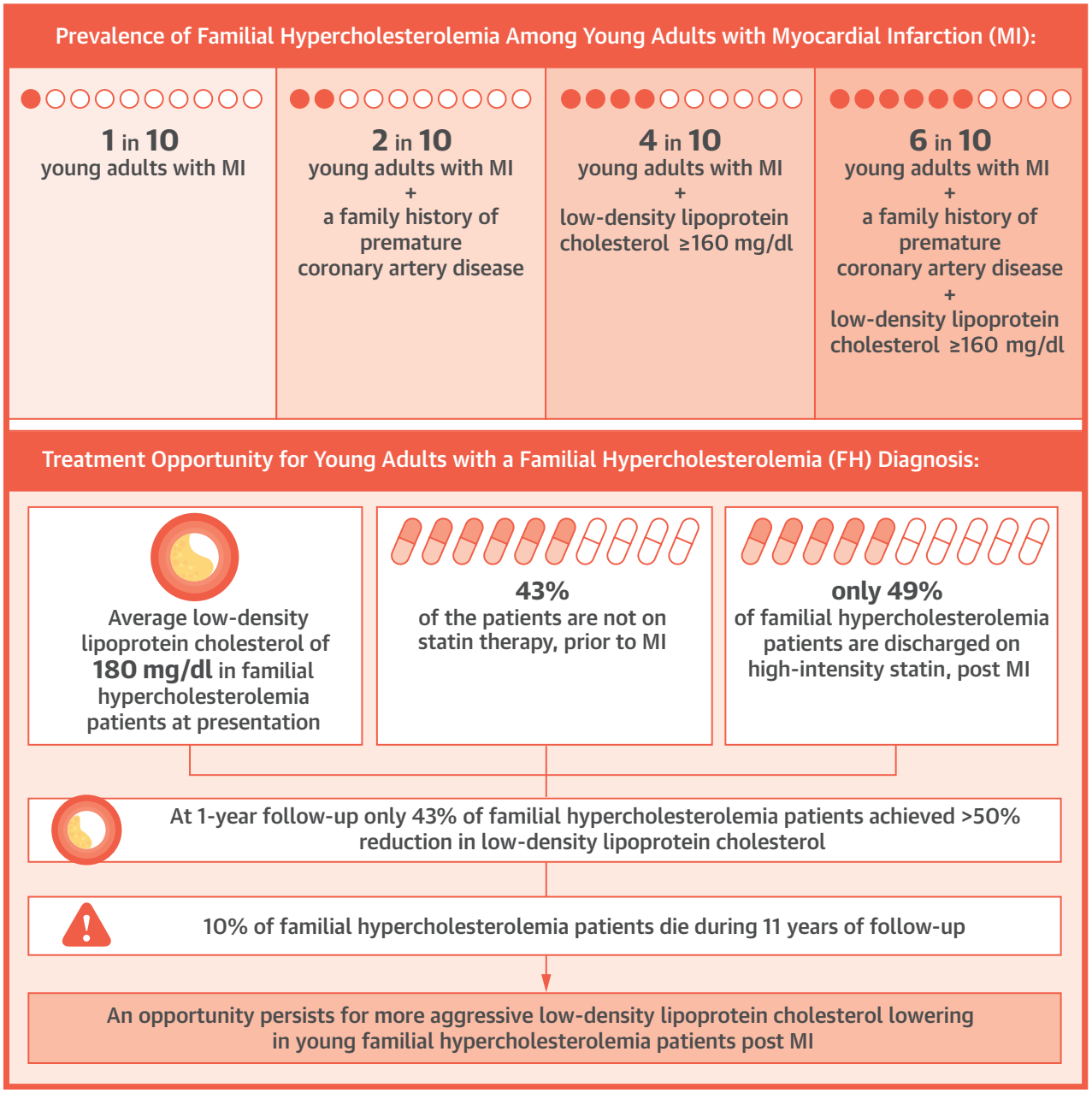
Although our paper focused on patients with FH, it is noteworthy that the observed underutilization of high-intensity statins was present for both FH and non-FH patients. Our findings are in keeping with recent national data suggesting that young adults in general are significantly less likely to be prescribed high-intensity statins after an MI, compared with older age groups (30–35). Continued focus on optimizing lipid lowering for at-risk patients is needed (36,37).

Even though statin therapy was not at an optimal level, it is noteworthy that a significantly higher proportion of FH patients were on statin therapy prior to their MI when compared with the non-FH group (57% vs. 10%). The increased use of statins by this group may be due to primary prevention efforts prompted by guideline recommendations for the treatment of patients with severe hypercholesterolemia (LDL-C 190 mg/dl or higher) regardless of the presence of FH.

Although our findings focus on reduction in LDL-C, it is important to also control other risk factors in FH and non-FH patients who experienced an MI at a young age, such as treatment of hypertension and tobacco use. In our study, hypertension was more prevalent among patients with FH compared with non-FH, as has also been reported in other cohorts (3,4). Active smoking was present in 51% of our cohort and was similar for both FH and non-FH patients. Interestingly, smoking in patients with FH is associated with a 2-fold increase in the rate of cardiovascular events (38), a finding that reinforces the need for aggressive measures for smoking cessation in such patients.

PROGNOSIS OF FH PATIENTS. Our study did not show a significant difference in all-cause or cardiovascular mortality over long-term follow-up. Although this is the largest study of FH patients with MI at age ≤50 years with follow-up of >10 years, our study was underpowered for this analysis given the low rate of fatal events in this young population. Studies from older cohorts have shown the significantly worse prognosis of FH patients compared with those without FH. In an analysis from the Swiss SPUM-ACS cohort, FH patients had a significantly higher rate (adjusted HR: 3.53; p = 0.02) of recurrent cardiovascular events over 1-year follow-up (39). Similarly, in the Arabian Gulf cohort, the authors observed a higher rate of cardiovascular events among FH patients over 1 year (23). The lower event rate in our study could also have been related to the

CENTRAL ILLUSTRATION **Prevalence of Familial Hypercholesterolemia Across Subgroups**



Singh, A. et al. J Am Coll Cardiol. 2019;73(19):2439-50.

The prevalence of familial hypercholesterolemia (FH) across subgroups of young adults who experienced a myocardial infarction. Each **circle** represents 10% of the population. Proportion with FH shown by the **red circles.**

lower residual LDL-C achieved compared with other cohorts (39) as well the fact that our study only examined differences in mortality while other studies also included nonfatal cardiovascular endpoints.

ROLE OF GENETIC TESTING. Khera et al. (40) evaluated the risk of CAD across strata of LDL-C and found an FH mutation in only 1.7% of patients with LDL-C ≥190 mg/dl. However, mutation carriers were at much higher risk compared with noncarriers within

similar strata of LDL-C, likely reflecting their prolonged exposure to elevated LDL-C levels (40). Do et al. (41) evaluated FH mutations in a large cohort of patients with an early MI (defined as men age ≤50 and women age ≤60 years) and found a mutation in the *LDLR* gene in 3.1% of patients. In contrast, Amor-Salamanca et al. (19) found an FH mutation in 8.7% ACS patients age <65 years, but their study only included individuals with an LDL-C ≥160 mg/dl. The authors further found that 27% of patients met DLC criteria for definite/probable FH, which is very similar to the 36% observed in the same subgroup (i.e., LDL-C ≥160 mg/dl), especially when considering the younger age of our cohort.

Because patients with FH mutations are at higher risk, young adults with probable/definite clinical criteria for FH may benefit from genetic testing, especially given the availability of newer therapies, such as PCSK9 inhibitors, and the fact that risk among FH patients remains highly variable (42). Nevertheless, as also suggested by guidelines, all patients with severe elevation in LDL-C should be treated with high-intensity statins, even if genetic testing was not performed or is negative, especially among those who experienced a cardiovascular event at a young age (7,13,43,44).

When considering the role of genetic testing, our study provides data on subgroups of patients that may have a higher yield for such testing (**Central Illustration**). In addition to genetic testing, cascade screening of patients identified with a monogenic cause of hyperlipidemia should be performed, as several studies have shown this to be a cost-effective approach (45–47).

STUDY LIMITATIONS. We defined FH based on clinical criteria, as genetic testing results were not routinely performed, and patients may have elevations in LDL-C due to polygenic or mixed hyperlipidemia. However, most other studies also lack genetic testing, (3,10,23,39), as such testing is rarely performed in most clinical settings. Furthermore, among those with severe LDL-C elevation, intensive statin therapy is indicated regardless of mutation prevalence. A strength of our study is that we included information on physical examination findings, which was not common in other cohorts. Although our study design did not allow us to confirm whether such findings were present or absent in every case, examination for corneal arcus and tendon xanthomas should be performed in all patients with premature cardiovascular disease or severe hyperlipidemia.

Our study used the DLC criteria for our primary analysis. Although it is less sensitive than the Simon Broome criteria, it is more specific and has been widely used in most other recent cohorts, enabling comparison with other studies. Nevertheless, even the DLC criteria may fail to identify some patients with FH, especially when using a retrospective study design. Furthermore, we were not able to confirm the presence of premature events in first-degree relatives, as has been done in some nationwide registries. Also, our criteria for classification of premature events in first-degree female relatives were set at age 65 years compared to age 60 years used in the DLC criteria, which may bias the estimated prevalence of FH.

We estimated untreated LDL-C whenever pretreatment LDL-C levels were not available for patients on lipid-lowering therapy prior to MI. Although such a correction has been used in most studies, we used the specific type and dose of lipid-lowering therapy rather than relying on a fixed correction factor regardless of the dose (3,4,23), which may over or underestimate LDL-C. Because Lp(a) was only rarely measured in our cohort, we were unable to evaluate the frequency of elevated Lp(a) in our population, or to calculate the corrected LDL-C level in the subset of patients who may have severely elevated Lp(a). Also, we did not evaluate for secondary causes of hyperlipidemia, such as hypothyroidism or nephrotic syndrome. Finally, the YOUNG-MI registry excluded patients with prior CAD; therefore, it is possible that the true prevalence of FH may be underestimated.

CONCLUSIONS

Clinically defined FH is present in nearly 1 in 10 patients with MI under the age of 50 years. Among this group, only 63% are discharged on high-intensity statin therapy, and the vast majority have elevated LDL-C at 1 year, with 43% having LDL-C ≥100 mg/dl and 82% having LDL-C ≥70 mg/dl. Even among non-FH patients who experienced an MI at a young age, 25% had LDL-C ≥100 mg/dl and 65% had LDL-C ≥70 mg/dl. Our findings highlight the need for more aggressive lipid-lowering therapy in both young FH and non-FH patients post-MI.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a cohort of patients with probable or definite FH in whom MI developed before age 50 years, one-third were discharged from hospital without a high-intensity statin therapy, and the majority had elevated LDL-C levels 1 year later.

TRANSLATIONAL OUTLOOK: Improved methods are needed to detect and more aggressively manage young patients with FH.

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KEY WORDS acute coronary syndrome, ezetimibe, familial hypercholesterolemia, myocardial infarction, PCSK9, prevention, statins, young adult

APPENDIX For supplemental figures and tables, please see the online version of this paper.