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# Prevalence, risk factor burden, and severity of coronary artery disease in patients with heterozygous familial hypercholesterolemia hospitalized for an acute myocardial infarction: Data from the French RICO survey

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28 **ABSTRACT**

29 **BACKGROUND:** Individuals with heterozygous familial hypercholesterolemia (FH) are at  
30 high risk of early myocardial infarction (MI). However, coronary artery disease (CAD) burden  
31 of FH remains not well described, especially for French patients.

32 **OBJECTIVE:** To assess the prevalence of FH and severity of CAD from a large database of  
33 a French regional registry of acute MI.

34 **METHODS:** All consecutive patients hospitalized for an acute MI in a multicenter database  
35 from 2001-2017 were considered. FH was diagnosed using an algorithm adapted from the  
36 Dutch Lipid Clinic Network criteria. The prevalence and clinical features of FH, and the  
37 severity of CAD were assessed.

38 **RESULTS:** Among the 11624 patients included in the study, the proportion of  
39 "probable/definite", "possible", and "unlikely" FH in patients with MI was 2.1% (n=249), 20.7%  
40 (n=2405), and 77.2% (n=8970). When compared with patients "unlikely" FH, patients with  
41 "probable/definite" FH were 20 years younger (51 vs 71,  $p<.001$ ), with a lower rate of  
42 diabetes (17% vs 25%,  $p=.007$ ) and a higher prevalence of personal and familial history of  
43 CAD. Chronic statin treatment was only used in 48% of FH patients and ezetimibe in 8%.  
44 After adjustment for age, sex and diabetes, FH patients were characterized by increased  
45 extent of CAD (SYNTAX score 11 vs 7,  $p<.001$ ) and multivessel disease (55% vs 40%,  
46  $p<.001$ ).

47 **CONCLUSIONS:** In this large cohort of French individuals, FH was common in patients with  
48 MI, associated with markedly early age of MI and severity of CAD burden and limited use of  
49 preventive lipid lowering therapy.

50

## 51 **INTRODUCTION**

52 Heterozygous familial hypercholesterolemia (FH) is an autosomal co-dominant genetic  
53 disease associated with significantly increased risk of atherosclerotic cardiovascular disease  
54 including myocardial infarction (MI) [1,2]. The prevalence of heterozygous FH has been  
55 estimated to be 1:250 individuals in Western populations [3,4]. In the general population, FH  
56 is underdiagnosed and, for many FH patients, the initial clinical manifestation is the  
57 occurrence of an acute coronary syndrome (ACS) [1,5]. As a consequence, the prevalence  
58 of FH is considerably higher among patients hospitalized for ACS compared with the general  
59 population [6-13].

60 Several recent studies have determined the prognostic impact of FH in patients after a first  
61 ACS [9,12-15]. However, the severity of coronary artery disease (CAD) has been poorly  
62 described in patients with FH hospitalized for an acute MI [16]. Moreover, no data are  
63 available on the prevalence and characteristics of French patients with FH and hospitalized  
64 for MI. The detection of FH at time of an acute coronary event is not systematically  
65 performed in France, although these patients are at high risk of recurrence of cardiovascular  
66 events [17].

67 Therefore, in the present study, we aimed to investigate the prevalence of FH, the risk factor  
68 burden and the severity of CAD at the time of admission in a coronary care unit (CCU) from a  
69 large database of a regional French registry (RICO registry) of patients with acute MI.

70

## 71 **METHODS**

### 72 **Study population**

73 This study was performed with the framework of the RICO (obseRvatoire des Infarctus de  
74 Côte d'Or) survey designed to include all consecutive  $\geq 18$  years patients hospitalized for an  
75 acute MI since 2001 in a multicenter registry of all the CCU of the region of Côte d'Or in  
76 France. Details regarding the methods of the RICO survey were previously reported [18].  
77 Briefly, baseline characteristics including demographic data, risk factors, treatments for  
78 hypercholesterolemia, family history of CAD (defined as premature CAD in first-degree  
79 relative  $< 55$  years for men or 65 years for women), cardiovascular history and chronic  
80 treatments were prospectively collected. At admission, the following data were also collected:  
81 Killip class, ECG signs and hemodynamic parameters (heart rate (HR), systolic (SBP) and  
82 diastolic (DBP) blood pressure). Left ventricular ejection fraction (LVEF) was measured by  
83 echocardiography  $< 12$ h following admission. Blood sample was taken at admission for lipid  
84 profile. Hospital complications were determined and delays in time to admission as well as  
85 prolongation of stay in CCU). For each patient, GRACE (Global Registry of Acute Coronary  
86 Events) risk score, as a tool to assess mortality risk in acute MI ([http://www.outcomes-umassmed.org/grace/acs\\_risk/acs\\_risk\\_content.html](http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html)) and SYNTAX (SYNergy between PCI

88 with TAXus and cardiac surgery trial) score, as an index of CAD severity, were calculated  
89 [19,20].

90 Patients were recruited consecutively after obtaining written informed consent, with the  
91 exception of patients who died in the first hours after admission or with a severe cardiogenic  
92 shock. The study was conducted in compliance with Good Clinical Practice guidelines and  
93 the French data protection law. The protocol was approved by the Dijon University Hospital  
94 Committee for the Protection of Human Subjects and was declared to the Commission  
95 Nationale Informatique et Liberté.

96 For this study, 11 624 consecutive patients hospitalized between 2001 and 2017 were  
97 recruited.

98

### 99 **Diagnosis of familial hypercholesterolemia**

100 All patients were assessed for the presence of FH based on the Dutch Lipid Clinic Network  
101 (DLCN) criteria [21], recommended by guidelines to diagnose FH in the general population in  
102 central European countries [1, 22]. The score was calculated using points from the following  
103 criteria: premature family history of CAD for a first-degree relative (at age < 55 years for men  
104 and < 60 years for women; 1 point); premature personal history of CAD (2 points) or vascular  
105 disease (1 point); and plasma low-density lipoprotein cholesterol (LDL-C > 330 mg/dL (8  
106 points), 250-329 mg/dL (5 points), 190-249 mg/dL (3 points), 155-189 mg/dL(1 point). In  
107 individuals on lipid-lowering therapy, LDL-C on admission was corrected according to type of  
108 agents: statin (+30%), ezetimibe (+20%), statin and ezetimibe (+40%). The choice for a  
109 conservative correction factor for statin therapy (+30%) is driven by the preferential use of  
110 moderate intensity statin in France. The presence of tendon xanthomas or corneal arcus,  
111 family history of hypercholesterolemia or vascular disease were not recorded in the  
112 database. Missing information was counted as zero, as done in previous studies [6,9,15]. A  
113 probable/definite FH diagnosis was considered when the DLCN score was  $\geq 6$ , a possible  
114 diagnosis when the score was 3-5 and unlikely when the score was < 3 points. The group of  
115 patients with probable/definite FH was compared with the group unlikely FH, called "no"FH.

116

### 117 **Statistical analysis**

118 Characteristics of patients are presented as median (interquartile range) for continuous  
119 variables and number (percentage) for categorical variables. Dichotomous variables were  
120 expressed as n(%) and continuous variables as median [interquartile range]. A Kolmogorov-  
121 Smirnov test was performed to analyse the normality of continuous variables. Mann-Whitney  
122 test was used to compare continuous data, and the Chi 2 test or Fisher's test was used for  
123 dichotomous data. The threshold for significance was set at 5%. In addition to the full cohort,  
124 a matched subset was built, with one FH patient matched with three patients without FH,

125 based on age ( $\pm$ SD in whole population), sex and diabetes mellitus. For matching data, the  
126 Wilcoxon test was used instead of the Mann-Whitney test. SPSS version 12.0.1 (IBM Inc,  
127 USA) was used for all of the statistical tests.

128

## 129 **RESULTS**

130 Among 11624 patients hospitalized for acute MI, 249 (2.1%) had a probable/definite FH  
131 (score  $\geq$  6), 2405 (20.7%) a possible FH (score 3-5) and 8970 (77.2%) no FH (score < 3).  
132 The baseline characteristics of patients with (probable/definite) FH and without (no) FH are  
133 reported on *Table 1* for the whole population (called "Full cohort") and for the 2 matched  
134 cohorts built after adjustment for age, sex and diabetes (called "Matched subset").

135 The "probable/definite" FH groups was  $\approx$  20 years younger ( $p < .001$ ), had a higher BMI  
136 ( $p = .016$ ), a greater prevalence of smoking ( $p < .001$ ), premature CAD ( $p < .001$ ), family history  
137 of CAD ( $p < .001$ ), but a lower prevalence of diabetes ( $p = .007$ ), hypertension ( $p < .001$ ) and  
138 stroke ( $p = .016$ ). However after adjustment for age, sex and diabetes, the prevalence of  
139 hypertension was higher for patients with probable/definite FH ( $p = .002$ ), and the history of  
140 stroke does not differ between the two groups, whereas patients with probable/definite FH  
141 have more history of peripheral artery disease ( $p = .018$ ). After adjustment, the proportion of  
142 smokers was similar in the two groups.

143 As expected, median LDL-C was about twice as high (207 vs 112 mg/dL) for patients with  
144 probable/definite FH and more patients with probable/definite FH were receiving lipid-  
145 lowering medications. However chronic statin treatment was only used in 48% of  
146 probable/definite FH patients and only 8% were receiving ezetimibe. The characteristics of  
147 the untreated versus treated patients with probable/definite FH are summarized on Suppl.  
148 *Table 1*: globally, a treatment was more frequent for the categories of patients at the highest  
149 risk (higher prevalence of patients with previous CAD, with diabetes and with hypertension  
150 for patients on lipid-lowering treatment). Patients with probable/definite FH and previous CAD  
151 are more likely to receive either statin therapy (84% in the full cohort and 87% in the matched  
152 subset) or ezetimibe treatment (25% in the full cohort and 32% in the matched subset). On  
153 the other hand, the coronary angiography data are similar in FH patients with and without  
154 treatment.

155 *Table 2* shows data on coronary lesions at coronary angiography and *Table 3* data on in-  
156 hospital outcomes. After adjustment (post-matching data), the use of coronary angiography  
157 was similar for patients with and without FH. The GRACE risk score was lower for patients  
158 with probable/definite FH in both pre- and post-matched cohorts. However, after adjustment  
159 for age, sex and diabetes, patients with probable/definite FH were characterized by  
160 increased extent of CAD (SYNTAX score 11 vs 7,  $p < .001$ ) (*Figure 1*) and multivessel disease

161 (55% vs 40%,  $p<.001$ ) (*Figure 2*) (*Table 2*). After adjustment, no significant differences  
162 appear on in-hospital outcomes (*Table 3*).

163

## 164 **DISCUSSION**

165 FH subjects are at high risk for acute MI, and characterization of CAD burden and FH pre  
166 valence in MI population are key issues for management strategies. In this large population-  
167 based study, we show that about 2% of acute MI patients had FH, and these patients were  
168 characterized by their young age, severity of CAD disease and dramatic underuse of lipid-  
169 lowering therapies.

170 As patients with FH have an increased risk of CAD compared to unaffected individuals, the  
171 prevalence of FH in patients hospitalized for an acute MI should be higher than estimated in  
172 the general Western populations (ie. 1 to 250 individuals). The prevalence of FH has not yet  
173 been reported in French patients hospitalized for ACS and in the present study, we show a  
174 prevalence 5-fold higher among patients hospitalized for an acute MI compared with the  
175 expected prevalence in the general population. The prevalence of 2.1% of probable/definite  
176 FH in this large database is in excellent agreement with data obtained in Switzerland (1.6%  
177 in the SPUM-ACS cohort) [6] and in Denmark (2.0% in patients with first MI) [10]. The higher  
178 prevalence reported in Australia by Pang et al. [8] could be due to the larger correction factor  
179 used for adjustment of LDL-C in individuals on statins associated with a larger use of statins  
180 (68% vs 48%). Indeed the mean correction factor was 2.0 in the study from Pang et al. [8]  
181 and only 1.48 in our study. The high prevalence (8.3%) found in EUROASPIRE IV [7] could  
182 be a reflection of the differences in recruitment methodology. As for the Danish cohort [10],  
183 all patients hospitalized for an acute MI were included in our consecutive study.

184 A study conducted in the Arabian Gulf using the same corrected factor for prior statin use  
185 has reported a higher prevalence 3.7% [12], close to Chinese data [11,13]. An elevated rate  
186 of consanguinity among Gulf citizens has been suggested as explanation [12]. As already  
187 reported in several cohorts [2], the characteristics of patients with FH hospitalized for MI  
188 differ from patients without FH: they were younger (20 years younger in our cohort), had a  
189 higher prevalence of premature CAD and family history of CAD, and had lower incidence of  
190 diabetes. A lower prevalence of diabetes in FH has been well described in the Netherlands  
191 by comparing FH patients and their non-affected relatives [23]. In our study, after adjustment  
192 for age, sex and diabetes, patients with FH were more frequently hypertensive and had a  
193 higher prevalence of peripheral artery disease, in agreement with an increased risk recently  
194 reported for FH patients [24]. The GRACE risk score was found lower for patients with FH,  
195 even after adjustment, in agreement with other reports [12,14].

196 Patients with FH hospitalized for ACS or MI have a worse prognosis as already described in  
197 several populations, with an approximate 2-fold increased risk for recurrence of coronary or

198 other cardiovascular events [12,14,15]. By contrast, few data are available on the severity of  
199 the disease at the time of admission in a CCU: in a small cohort of 16 patients with FH  
200 compared to 27 non-FH patients, Yasuda et al. [16] reported that the FH group more  
201 frequently had multiple-vessel disease while the non-FH group was likely to have single-  
202 vessel disease. Multivessel CAD was also found more common in two other studies,  
203 however conducted in patients with only possible FH [9,13]. Recently, Li et al. [25] have used  
204 the Gensini scoring system to assess the severity of CAD and reported an increase in the  
205 severity of CAD in Chinese patients with FH. Our data from a large cohort show a significant  
206 increase of multivessel CAD in patients with probable/definite FH versus no FH patients.  
207 Moreover, the severity of CAD for FH patients is confirmed by a significant increase of the  
208 SYNTAX Score. These results were observed despite a greater use of statin therapy in the  
209 FH group, and reflected the high cumulative LDL-C burden associated with FH.  
210 Several limitations need to be considered in the present study: First, there are missing data  
211 regarding the presence of tendon xanthomas or corneal arcus, and high cholesterol levels in  
212 the first degree family members; therefore the prevalence can be underestimated. The  
213 genetic testing was not performed to confirm the FH diagnosis. Nevertheless, our procedure  
214 for identifying FH has been employed in numerous previous publications [6-15]. Second, the  
215 statin doses were not reported in this study and the LDL-C levels for FH diagnosis might  
216 have a degree of bias. However, we have adjusted LDL-C levels by a relatively low  
217 correction factor corresponding to a 30% LDL-C decrease on statin treatment to avoid an  
218 overestimation of patients with probable/definite FH. Moreover, we have only compared  
219 patients with probable/definite FH with patients unlikely FH. In addition to the size of the  
220 cohort, a strength of this study is the recruitment of all consecutive patients hospitalized for  
221 an acute MI in a French region.

222

## 223 **CONCLUSIONS**

224 In a large cohort from a French region, we found a high prevalence of FH in real world  
225 patients hospitalized for an acute MI. Patients with FH were associated with a greater  
226 severity of CAD burden. Despite a greater use of lipid-lowering therapy compared with  
227 patients without FH, about half of patients with FH were not receiving statin therapy before  
228 the acute event. This study confirms that FH is underdiagnosed and undertreated and  
229 strategies to optimize the identification and the management of FH patients should be  
230 advocated.

231

232

233



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239

240 **Authors' contributions**

241 MF, HY, PB, DB contributed to the conception or design of the work.

242 FC, MM, FB, PB, DB contributed to the acquisition, analysis, or interpretation of data for the  
243 work.

244 MF, MZ drafted the manuscript.

245 MZ, YC, FC, critically revised the manuscript.

246 JCB, CSV, YC, MZ finally approved the manuscript

247 All authors approved the present article.

248

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256

257

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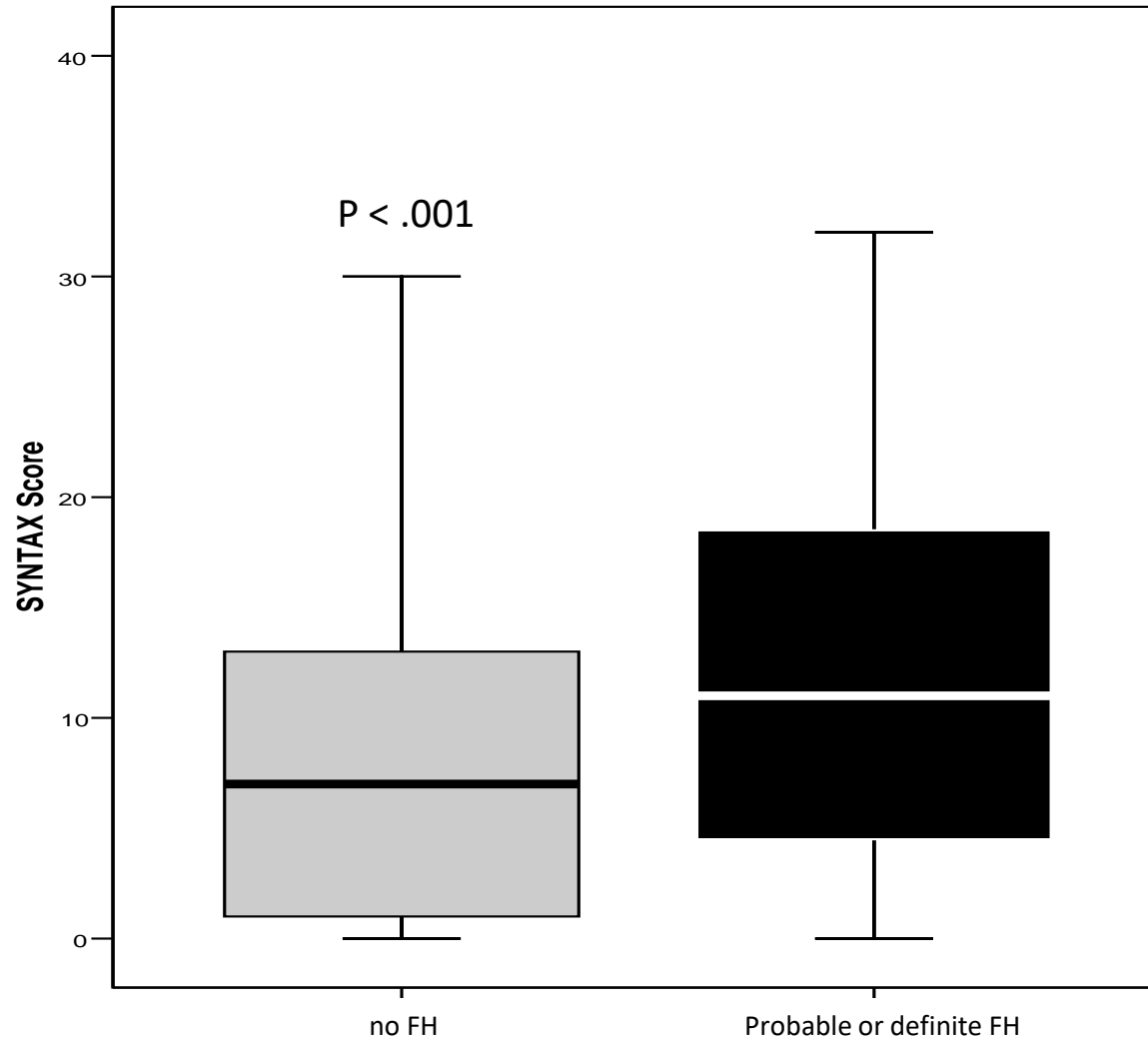
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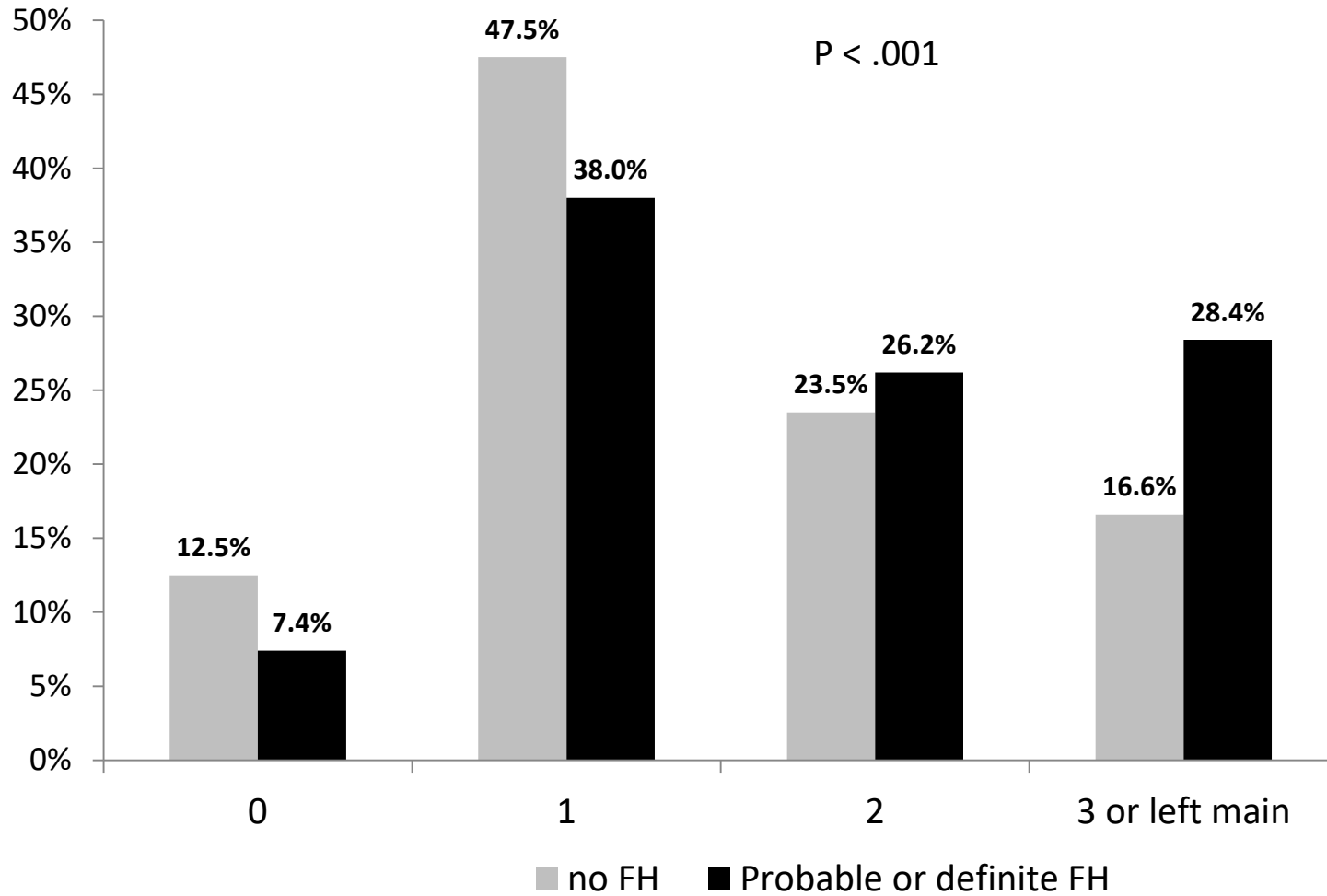
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**Figure 1: Severity of CAD assessed by SYNTAX Score for patients with and without FH**



**Figure 2: Number of significant coronary lesions for patients with and without FH**



**Table 1: Characteristics of patients at admission for acute MI with and without FH: data from full cohort and matched subset**

n (%) or median (IQR)	Full cohort			Matched subset		
	no FH (n=8970)	Probable/definite FH (n=249)	P value	no FH (n=699)	Probable/definite FH (n=233)	P value
<u>Patient characteristics</u>						
Age (years)	71 (61-80)	51 (46-57)	<.001	51 (46-57)	51 (46-57)	.993
Female	2799 (31%)	78 (31%)	.967	216 (31%)	72 (31%)	1
BMI (kg/m <sup>2</sup> )	26 (24-29)	27 (24-30)	.016	26 (23-30)	27 (24-30)	.092
Diabetes	2215 (25%)	43 (17%)	.007	117 (17%)	39 (17%)	1
Hypertension	5304 (59%)	117 (47%)	<.001	243 (35%)	107 (46%)	.002
Current smoking	2098 (23%)	140 (56%)	<.001	390 (56%)	128 (55%)	.819
<u>Comorbidities</u>						
Previous CAD*	1290/8909 (15%)	49/248 (20%)	.020	50/687 (7%)	37/232 (16%)	<.001
Premature CAD	1207/8304 (15%)	201/245 (82%)	<.001	535/687 (78%)	188/229 (82%)	.175
Family history of CAD	1619 (18%)	195 (78%)	<.001	33 (5%)	184 (79%)	<.001
Stroke	693/8910 (8%)	9/247 (4%)	.016	28/695 (4%)	7/231 (3%)	.491
PAD	479/8914 (8%)	20/247 (8%)	.864	23/696 (3%)	16/231 (7%)	.018
<u>Lipid-lowering medications</u>						
Statins	2078 (23%)	119 (48%)	<.001	91 (13%)	107 (46%)	<.001
Ezetimibe	156 (2%)	20 (8%)	<.001	5 (1%)	20 (9%)	<.001
Fibrates	490 (6%)	4 (2%)	.008	38 (5%)	4 (2%)	.018
<u>Biological data</u>						
TC (mg/dL)	184 (156-212)	284 (255-320)	<.001	190 (165-210)	284 (255-320)	<.001
LDL-C (mg/dL)	112 (88-136)	207 (175-241)	<.001	118 (96-136)	207 (176-238)	<.001
Corrected LDL-C ≥ 190 mg/dL	0	248 (99.6%)	<.001	0	232 (99.6%)	<.001
HDL-C (mg/dL)	44 (36-54)	43 (36-52)	.354	41 (33-51)	43 (36-52)	.021
TG (mg/dL)	114 (82-162)	152 (114-219)	<.001	131 (90-191)	150 (113-217)	<.001
<u>Clinical data</u>						
Blood pressure (BP), mmHg						
Systolic BP	139 (120-159)	140 (126-161)	.018	134 (119-153)	140 (126-161)	<.001
Diastolic BP	80 (69-90)	85 (76-99)	<.001	80 (70-94)	85 (77-99)	<.001
LVEF (%)	53 (43-60)	55 (45-61)	.039	55 (45-61)	55 (45-62)	.905
Heart failure	2291 (26%)	42 (17%)	.002	100 (14%)	37 (16%)	.557
STEMI	4841 (54%)	130 (52%)	.580	420 (60%)	123 (53%)	.050

\* Previous CAD: previous MI, unstable angina, coronary artery bypass grafting or percutaneous coronary intervention

TC: total cholesterol; LDL-C: LDL cholesterol; HDL-C: HDL cholesterol; TG: triglycerides; STEMI: ST-segment elevation myocardial infarction; PAD: peripheral artery disease; BMI: body mass index; IQR: interquartile range; LVEF: left ventricular ejection fraction

**Table 2: Coronary lesions for patients with and without FH: data from full cohort and matched subset**

n (%) or median (IQR)	Full cohort			Matched subset		
	no FH (n=8970)	Probable/ definite FH (n=249)	p value	no FH (n=699)	Probable/ definite FH (n=233)	p value
Coronary angiography	8465 (94%)	244 (98%)	.014	682 (98%)	229 (98%)	.524
GRACE risk score	151 (128-177)	112 (96-134)	<.001	118 (102-140)	111 (97-134)	.015
SYNTAX score	10 (5-18)	11 (5-19)	.622	7 (1-13)	11 (4-19)	<.001
Multivessel disease	4504/8465 (54%)	134/244 (55%)	.691	273/682 (40%)	125/229 (55%)	<.001

**Table 3: In-hospital outcomes for patients with and without FH: data from full cohort and matched subset**

n (%)	Full cohort			Matched subset		
	no FH (n=8970)	Probable/ definite FH (n=249)	p value	no FH (n=699)	Probable/ definite FH (n=233)	p value
Recurrent MI	466 (5.2%)	11 (4.4%)	.584	42 (6.0%)	10 (4.3%)	.323
Stroke or TIA	129 (1.4%)	3 (1.2%)	1	4 (0.6%)	3 (1.3%)	.376
CV death	483 (5.4%)	3 (1.2%)	.004	17 (2.4%)	3 (1.3%)	.296
Death	546 (6.1%)	3 (1.2%)	.001	18 (2.6%)	3 (1.3%)	.251
Heart failure	2842 (32%)	50 (20%)	<.001	127 (18%)	45 (19%)	.697