Coronary lesion complexity in patients with heterozygous familial hypercholesterolemia hospitalized for acute myocardial infarction: data from the RICO survey

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Abstract

Background: Although patients with familial heterozygous hypercholesterolemia (FH) have a high risk of early myocardial infarction (MI), the coronary artery disease (CAD) burden in FH patients with acute MI remains to be investigated.

Methods: The data for all consecutive patients hospitalized in 2012–2019 for an acute MI and who underwent coronary angiography were collected from a multicenter database (RICO database). FH (n = 120) was diagnosed using Dutch Lipid Clinic Network criteria (score ≥ 6). We compared the angiographic features of MI patients with and without FH (score 0–2) (n = 234) after matching for age, sex, and diabetes (1:2).

Results: Although LDL-cholesterol was high (208 [174–239] mg/dl), less than half of FH patients had chronic statin treatment. When compared with non-FH patients, FH increased the extent of CAD (as assessed by SYNTAX score; P = 0.005), and was associated with more frequent multivessel disease (P = 0.004), multiple complex lesions (P = 0.022) and significant stenosis location on left circumflex and right coronary arteries. Moreover, FH patients had more multiple lesions, with an increased rate of bifurcation lesions or calcifications (P = 0.021 and P = 0.036, respectively). In multivariate analysis, LDL-cholesterol levels (OR 1.948; 95% CI 1.090–3.480, P = 0.024) remained an independent estimator of anatomical complexity of coronary lesions, in addition to age (OR 1.035; 95% CI 1.014–1.057, P = 0.001).

Conclusions: FH patients with acute MI had more severe CAD, characterized by complex anatomical features that are mainly dependent on the LDL-cholesterol burden. Our findings reinforce the need for more aggressive preventive strategies in these high-risk patients, and for intensive lipid-lowering therapy as secondary prevention.

Keywords: Familial hypercholesterolemia, Myocardial infarction, Complex coronary lesions, LDL cholesterol
Introduction

Heterozygous familial hypercholesterolemia (FH) is one of the most common autosomal dominant genetic diseases [1], with an estimated prevalence of 1/250 in Western countries. It is characterized by high levels of LDL cholesterol (LDL-C) [2, 3], resulting in most cases from a mutation of the LDL receptor (LDL-R), apolipoprotein B (apoB), or proprotein convertase subtilisin/kexin type 9 (PCSK9). The most commonly used routine diagnostic criteria are the Dutch Lipid Clinic Network (DLCN) criteria, based primarily on elevated LDL-C levels and the presence of a family and personal history of premature coronary heart disease [4]. In uncertain cases, a genetic analysis can be used to confirm the diagnosis and to provide sensitive and specific molecular family screening.

Patients with FH present a very high cardiovascular (CV) risk and are therefore exposed to the occurrence of coronary events at an early age [5, 6]. On average, patients with FH have a risk of early coronary artery disease (CAD) that is 13 times higher than in the general population [5]. When individuals do not respond to treatment, fatal or non-fatal coronary events occur in approximately 50% of men < 50 y and 30% of women < 60 y [6]. FH is often found after an individual has a myocardial infarction (MI), with an estimated prevalence between 1.6 and 4.3% [7, 8]. Furthermore, FH patients have an unfavorable prognosis after MI, with a risk of recurrence of cardiovascular or coronary events that is 2 to 3 times higher than the average [9, 10]. However, there are wide variations in the extent of CAD and in the level of coronary calcifications between individuals with genetically determined FH, suggesting the need for a better understanding of its specificities [4, 11].

Thus, while the clinical course of these patients is relatively well known, there is a paucity of research focused on the associated coronary lesions. Although CAD is more frequently associated with multi-vessel disease in FH patients, there are significant variations in prevalence [12–14]. Using the Gensini angiographic score, Wang [8] and Li [15] showed that CAD was more severe in patients with FH than in those without FH (according to the DLCN criteria). Findings from a series of 104 asymptomatic age-matched patients found that coronary lesions in CAD patients with genetically confirmed heterozygous FH are more diffuse and calcified than in patients without a genetic mutation [16]. The angiographic characteristics of the anatomical complexity of coronary lesions, such as number, size, lesion length, and multiple lesions are risk factors that worsen prognosis after MI [17, 18]. In addition, targeted therapeutic strategies appear to be more beneficial in patients with complex coronary anatomy [19]. However, the complexity of coronary lesions in symptomatic patients with FH has not yet been described.

The objective of this study was therefore to characterize the severity and complexity of coronary lesions on coronary angiography in FH patients hospitalized for acute MI.

Patients and methods

Study population, selection criteria

This retrospective study was conducted using data from the RICO (Côte d’Or Myocardial Infarction Observatory) database [20]. RICO is an ongoing survey that has included all consecutive patients aged at least 18 years hospitalized for an acute MI in a coronary care unit of all public or privately funded hospitals receiving MI emergencies in the region of Côte d’Or (France) since 2001. Cases were ascertained by the prospective collection of consecutive admissions. MI was identified by an increase in serum troponin I (greater than the upper limit of normal for each hospital) and clinical symptoms of ischemia and/or characteristic electrocardiographic signs.

For the current study, patients hospitalized for an acute MI at the Dijon University Hospital and who underwent coronary angiography between 2012 and 2019 were included. A retrospective analysis of coronary angiographies was performed using a digital medium (Intellispace Cardiovascular”). Acute MI was defined according to the current universal definition [21].

The probability of FH was calculated from the sum of the points from an adapted version of the Dutch Lipid Clinic Network (DLCN) score criteria [4]: family history of premature CAD in a first-degree relative (male < 55 years and female < 60 years; 1 point); personal history of premature CAD (2 points) or vascular disease (1 point); and LDL-cholesterol (LDL-C) value: 330 mg/dL [5 points], 190–249 mg/dL [3 points], 189 mg/dL [1 point]). In individuals on lipid-lowering therapy, LDL-C at admission was corrected for the drug class: statins (130%), ezetimibe (120%), and statins and ezetimibe (140%). A conservative correction factor for statin treatment (130%) was chosen because moderate intensity statins are mostly used in France. The presence of tendon xanthomas or corneal arches and a family history of hypercholesterolemia or vascular disease were not recorded in the database. Missing information was counted as zero. For each patient, the diagnosis of FH was considered certain or probable when the total score was ≥6, and absent when the score was < 3.

Among the patients included in the RICO database, 120 were categorized as certain or probable FH (score ≥ 6) and 4243 as unlikely FH (non-FH; score < 3). The characteristics of the main cohort have already been described [7]. The 120 FH patients were matched (1:2) with 234 non-FH patients from the database based on age (± standard deviation), sex, and presence of type 2 diabetes. The flow chart is described in Fig. 1.
We analyzed risk factors, CV history (defined as history of MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), lipid-lowering medications, time to admission, clinical data at admission, and hospital complications. Left ventricular ejection fraction (LVEF) was assessed within 12 h of admission using the Simpson biplane method. Blood lipids and other biological parameters were obtained on admission, except for peak troponin Ic, which was determined from 3 samples taken at 8-h intervals in the first 24 h after admission. We also calculated the GRACE score for each patient [22] according to age, Killip class, systolic blood pressure, heart rate, ST segment changes, cardiac arrest on admission, creatinine levels and cardiac enzyme elevation.

Evaluation of coronary angiography lesions and patient management
Coronary angiography images were reviewed by two trained interventional cardiologists who were blinded to the patient’s group. There was a discrepancy in 7 cases, which were then adjudicated through a joint review.

Coronary angiography was considered normal when the angiographic images did not show any visible atheromatous plaque or spastic phenomena. Coronary lesions were considered non-significant for stenoses < 50% (and significant when stenoses were ≥ 50%). Depending on the number of diseased vessels (≥ 2.5 mm), multivessel CAD was considered when they were located on the left anterior descending artery and/or the diagonal branches, the left circumflex artery and marginal arteries, the right coronary artery (and/or the posterior interventricular or the left retro ventricular arteries), with or without involvement of the left main artery.
For each patient, initial SYNTAX scores (before the revascularization procedure) and residual SYNTAX scores (after the revascularization procedure) were calculated [23].

Complex lesions were identified according to pre-specified criteria from the CHAMPION-PHOENIX [24] and DAPT [18] studies: left main lesion, long lesion > 20 mm, multiple lesions (> 2 lesions per vessel), bifurcation lesion (with side branch > 1.5 mm), significant tortuosity (two between 45 and 90° or one greater than 90° in the vicinity of the lesion), thrombus, angulation, eccentricity, and stenting of a saphenous graft. Moderate calcifications (radio-opaque density during the cardiac cycle and affecting only on one edge of the vascular wall) or severe calcifications (radio-opaque density visualized even in the absence of cardiac movement before injection of the contrast agent and most often throughout the arterial wall) were identified. Multiple complex lesions were defined by the presence of several complex lesions [17].

Coronary angiographic data were collected: TIMI flow, culprit artery, number of diseased vessels, stents (number, diameter, length and type), and revascularization strategies (thrombectomy, PCI and CABG). In-hospital CV events were also analyzed (recurrent MI, stroke, or family history of CAD (< 0.001). Statins (< 0.001) and ezetimibe (< 0.001) were prescribed more often to FH patients. However, although LDL-cholesterol was high (208 [174–239] mg/dL), less than half of FH patients had a prescription for chronic statin treatment. As expected, FH patients had higher levels of LDL-C and triglycerides (< 0.001 for both). On admission, the rate of ST-segment-elevation MI was similar for both groups (P = 0.355), as was the GRACE risk score (P = 0.20).

The median length of stay in the coronary care unit was 4 [3–5] days for both groups. FH and no-FH patients had similar rates of in-hospital events (HF: 20 [16.7%] vs 41 [17.5%], P = 0.840; recurrent MI: 2 [1.7%] vs 3 [1.3%], P = 1; stroke: 1 [0.8%] vs 1 [0.4%], P = 1; death 1 (0.8%) vs 2 (0.9%), P = 1).

Angiographic data are shown in Table 2. The percentage of optically healthy coronary arteries was much less frequent in FH patients than in non-FH patients, 3% vs 10% (P = 0.029), respectively, and 4 FH patients had coronary arteries without stenosis. Compared to the non-FH group, patients in the FH group had a higher initial SYNTAX score (11 [6–20] vs 8 [3–15], P = 0.005) and more frequent multivessel disease (56% versus 40%, P = 0.01) (Fig. 2). In contrast, the residual SYNTAX score was comparable between the two groups (P = 0.47). In FH patients, significant lesions were more often located on left circumflex and marginal arteries (P = 0.028), right coronary (P = 0.041) and the left retro ventricular artery (P = 0.04). On the other hand, no difference was found for the location of the culprit artery (P = 0.213). The rate of PCI (P = 0.84) and the number of implanted stents (P = 0.96) were not significantly different between groups, but CABG was more common in FH patients (P = 0.037).

The number of coronary lesions and their complexity characteristics are reported in Table 3 and Fig. 3. There was no difference between the 2 groups on the overall distribution of the number of complex anatomical features (P = 0.129). However, there was a non-significant trend towards more multiple complex lesions (> 1) in FH patients (P = 0.053). Our findings indicate that FH patients had more multiple lesions (P = 0.022), bifurcation lesions (P = 0.017), and calcified lesions (P = 0.033) (Fig. 3). Finally, there was a trend in toward longer lesions FH patients (P = 0.053), but with less thrombotic burden (P = 0.056).
Table 1 Baseline characteristics. (n (%)) or median (IQR)

| CV risk factors                  | Dutch Lipid Clinic Network score 0–2 | Dutch Lipid Clinic Network score ≥ 6 | P     |
|----------------------------------|--------------------------------------|-------------------------------------|-------|
| Age, years                       | 52 (46–59)                           | 51 (46–59)                          | 0.925 |
| Female                           | 89 (38%)                             | 43 (36%)                            | 0.685 |
| BMI, kg/m²                       | 27 (23–30)                           | 27 (24–31)                          | 0.098 |
| Hypercholesterolemia             | 61 (26%)                             | 86 (72%)                            | < 0.001 |
| Hypertension                     | 87 (37%)                             | 65 (54%)                            | 0.002 |
| Diabetes                         | 45 (19%)                             | 17 (14%)                            | 0.235 |
| Smoking                          | 137 (59%)                            | 68 (57%)                            | 0.734 |
| Prior CAD                        | 17 (7%)                              | 25 (21%)                            | < 0.001 |
| Family history of CAD            | 13 (6%)                              | 87 (73%)                            | < 0.001 |
| Stroke                           | 14 (6%)                              | 7 (6%)                              | 0.955 |
| PAD                              | 6 (3%)                               | 6 (5%)                              | 0.232 |
| Medications on admission         |                                      |                                     |       |
| Ezetrol                          | 3 (1%)                               | 14 (12%)                            | < 0.001 |
| Fibrate                          | 8 (3%)                               | 1 (1%)                              | 0.283 |
| Statins                          | 31 (13%)                             | 56 (47%)                            | < 0.001 |
| Discharge medications            |                                      |                                     |       |
| Ezetrol                          | 4 (2%)                               | 12 (10%)                            | < 0.001 |
| Fibrate                          | 2 (1%)                               | 0 (0%)                              | 0.551 |
| Statins                          | 212 (91%)                            | 111 (93%)                           | 0.549 |
| Clinical data                    |                                      |                                     |       |
| HR, beats/min                    | 77 [66–90]; n = 228                  | 80 [70–94]; n = 118                 | 0.197 |
| SBP, mmHg                        | 139 ± 29; n = 228                    | 145 ± 26; n = 118                   | 0.048 |
| DBP, mmHg                        | 85 ± 20; n = 228                     | 90 ± 19; n = 117                    | 0.033 |
| Time to admission, min           | 171 [97–388]; n = 227                | 175 [93–429]; n = 113               | 0.964 |
| LVEF, %                          | 55 [45–60]; n = 233                  | 55 [45–60]                          | 0.617 |
| LVEF < 40%                       | 26 (11%)                             | 7 (6%)                              | 0.104 |
| GRACE Score                      | 116 [96–138]; n = 224                | 110 [93–131]; n = 115               | 0.200 |
| HF                               | 37 (16%)                             | 17 (14%)                            | 0.684 |
| STEMI                            | 133 (57%)                            | 62 (52%)                            | 0.355 |
| Anterior wall location           | 86 (37%)                             | 35 (29%)                            | 0.154 |
| Biological data                  |                                      |                                     |       |
| Total cholesterol, mg/dL         | 194 [169–214]                        | 285 [250–320]                       | < 0.001 |
| HDL cholesterol, mg/dL           | 47 [3658]                            | 45 [36–54]                          | 0.194 |
| LDL cholesterol, mg/dL           | 119 [95–138]                         | 208 [174–239]                       | < 0.001 |
| LDL cholesterol, corrected ≥ 190 mg/dL | 0 (0%)                       | 117 (98%)                           | < 0.001 |
| Triglycerides, mg/dL             | 125 [85–176]                         | 149 [103–221]                       | 0.001 |
| CRP ≥ 3 mg/L                     | 130 (56%)                            | 82 (68%)                            | 0.020 |

Data are expressed as n (%) or medians (IQR)

CRP = C-reactive protein, PAD = peripheral artery disease, BMI = Body Mass index, CAD = coronary artery disease, HF = Heart failure, HR = Heart rate, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, LVEF = Left ventricular ejection fraction, STEMI = ST segment elevation MI
In multivariate analysis, only age (OR 1.033; 95% CI 1.011–1.055) and LDL-cholesterol level (OR 2.141; 95% CI 1.161–3.949) were associated with lesion complexity (> 1 complex anatomical feature) after adjustment for gender, diabetes, chronic statin therapy, FH diagnosis, and a CRP ≥ 3 mg/L (Table 4). The presence of FH, which tended to be associated with multiple complex lesions in univariate analysis, did not persist after adjustment for LDL-C. Furthermore, given the close link between inflammation and hypercholesterolemia, we
tested the interaction between CRP and LDL-cholesterol in the multivariate model ($P$ interaction = 0.005). The introduction of this interaction did not alter the conclusions of the model. Table 5 shows the variables associated with multivessel disease. Neither FH nor LDL-C levels persist as predictors when adjusted for confounding factors. However, high CRP levels were strongly associated with the development of multivessel disease, as was age ($P = 0.004$ and $P = 0.002$, respectively).

Discussion

Only few studies have assessed the characteristics of coronary lesions in FH patients hospitalized for acute MI [7, 8, 12–15]. After matching for the main factors associated with CAD, the findings of this study suggest that the FH-associated high cholesterol burden, which starts at an early age, and inflammation are associated with CAD severity. Here, severe CAD is characterized by multivessel disease, a high SYNTAX score, and anatomical complexity features, including bifurcation lesions and calcified plaques (Fig. 4). These data are consistent with previous studies that included patients with genetically-determined FH [14, 16, 25].

Wang et al. [8] reported frequent multi-vessel lesions in FH patients, while non-FH patients had more frequent one-vessel CAD (multi-vessel CAD: 75.7% versus 34.1% and one-vessel CAD; 54.3% versus 21.6%, respectively, $P < 0.001$). This finding was also reported in 2 other studies, although in patients with possible FH [13, 14]. In a recent study of 382 young survivors ($\leq 40$ years old) of acute MI, patients with HF were three times more likely to have multiple vessel lesion location (36.2% versus 12.8%, $P = 0.011$) [26]. Similar to the current study, a small number of patients with angiographically healthy coronary arteries or with non-significant lesions were found, ($n = 4$), but these individuals were considerably less likely to be FH patients [12]. Two recent Chinese studies investigated CAD extension in FH patients [8, 15] using Gensini

Table 3 Anatomical complexity of the coronary lesions

| Number of complex characteristics | Dutch Lipid Clinic Network score 0–2 $N = 234$ | Dutch Lipid Clinic Network score $\geq 6$ $N = 120$ | $P$  |
|----------------------------------|---------------------------------------------|---------------------------------------------|------|
| 0                                | 56 (24%)                                    | 23 (19%)                                    | 0.129|
| 1                                | 65 (28%)                                    | 26 (22%)                                    |      |
| 2                                | 73 (31%)                                    | 37 (31%)                                    |      |
| 3                                | 25 (11%)                                    | 18 (15%)                                    |      |
| 4                                | 10 (4%)                                     | 11 (9%)                                     |      |
| 5                                | 4 (2%)                                      | 3 (2%)                                      |      |
| 6                                | 0 (0%)                                      | 2 (2%)                                      |      |
| 7                                | 1 (0.4%)                                    | 0 (0%)                                      |      |
| Multiple complex lesions (number $> 1$) | 113 (48%)                                   | 71 (59%)                                    | 0.053|

Data are expressed as n (%)
angiographic criteria [27], which is limited to severity of stenosis (estimated as a percentage), coronary plaque features and lesion location (proximal or distal). FH patients had more severe coronary injury [8, 15], and male sex was significantly associated with complex lesions, in agreement with previous studies [18, 24]. This work on a young FH population (mean age 51 years) further suggests that in addition to the LDL-C burden, inflammation plays a role in promoting the extension of CAD, as highlighted by higher CRP levels [28, 29].

To the best of our knowledge, this is the first study to use validated complexity criteria to evaluate the coronary lesions of FH subjects on coronary angiography [18, 24]. We found that the number of multiple complex lesions was mainly related to age and LDL-C levels. Moreover, bifurcated lesions, large calcifications, and the presence of multiple lesions were the key anatomical features characterizing complex CAD in FH patients. In asymptomatic FH patients, Pang et al. [16] also found more calcified plaques, especially on the left main artery, and a higher calcium score using coronary computed tomography (CT).

PCI are high-risk procedures when done in calcified and bifurcated lesions, and recent studies, including a meta-analysis, have shown that these complex features have a major impact on the recurrence of ischemic events and long-term mortality [30, 31]. Moreover, in randomized clinical trials, the lesion complexity score was an independent predictor of short- and medium-term ischemic risk. The CHAMPION-PHOENIX trial, which included 10,854 patients with chronic or acute coronary syndrome, showed that a combined endpoint of all-cause death, recurrent MI, new revascularization guided by an ischemia test, or stent thrombosis within 48 h after PCI, was significantly related to the identified number of lesion complexity features (OR 1.68, 95% CI 1.20–2.36; OR 2.78, 95% CI 2.00–3.87; and OR 3.23, 95% CI 2.33–4.48, P < 0.001, for 1, 2, and 3 complex features compared with no complex features, respectively) [24]. This association was observed up to 30 days of follow-up. In the DAPT study, patients with complex coronary anatomy (defined by the presence of at least 1 complexity criterion) had increased rates of major CV events (5.3% versus 3.5%; P < 0.001) and MI or

| Variable                  | Univariate OR (95% CI) | P    | Multivariate OR (95% CI) | P    |
|---------------------------|------------------------|------|--------------------------|------|
| Female (vs male)          | 0.800 (0.520–1.232)    | 0.311| 0.570 (0.346–0.940)      | 0.028|
| Age, per y                | 1.027 (1.009–1.045)    | 0.003| 1.035 (1.014–1.057)      | 0.001|
| Diabetes (vs no diabetes) | 1.150 (0.663–1.993)    | 0.620| 0.889 (0.481–1.642)      | 0.707|
| Prior CAD (vs no CAD)     | 1.584 (0.818–3.068)    | 0.173| –                        | –    |
| Chronic statins (vs no statins) | 0.822 (0.506–1.334) | 0.427| –                        | –    |
| FH (DLCN score ≥ 6 vs ≤ 2) | 1.246 (0.997–1.556)    | 0.053| 0.890 (0.628–1.259)      | 0.510|
| LDL cholesterol, Per g/L  | 1.759 (1.215–2.546)    | 0.003| 1.948 (1.090–3.480)      | 0.024|
| CRP ≥ 3 mg/L (vs CRP < 3 mg/L) | 1.590 (1.036–2.438) | 0.034| 1.366 (0.873–2.136)      | 0.172|

OR Odds ratio, CI confidence interval, FH familial hypercholesterolemia, DLCN Dutch Lipid Clinic Network, LDL Low density lipoprotein, CAD coronary artery disease, CRP C-Reactive Protein

Fig. 3 Complex anatomical characteristics of coronary lesions

Table 4 Logistic regression analysis to estimate lesion anatomical complexity (> 1 complex lesion)
stent thrombosis (3.9% versus 2.4%; \( P < 0.001 \)) within 1 year, but these differences did not persist beyond 12 months [18]. Further work is needed to determine whether these characteristics could impact the short-term prognosis of FH patients after MI.

A recent French study on the 2005 and 2010 cohorts of the FAST-MI registry showed that an LDL-C target may be difficult to achieve in FH patients with acute MI. Even though they received intensive lipid-lowering therapy at discharge (statin + ezetimibe), FH patients had much higher LDL-C levels than non-FH patients at 5 years of follow-up (123 mg/dL and 83 mg/dL respectively, \( P < 0.001 \)) [32]. In addition, and during intensive lipid-lowering treatment, FH patients had an increased risk of death, MI recurrence and stroke, even after adjustment for CV risk factors, suggesting the need for more aggressive management. On the other hand, and beyond LDL-C concentration, some factors such as female sex, high HDL-C levels, not smoking and elevated adiponectin may contribute to improved cardiovascular event-free survival in FH patients [33].

As secondary prevention, PCSK9 inhibitors such as alirocumab or evolocumab can be used to lower LDL-C and have demonstrated their clinical benefit in addition to intensive statin treatment [34]. Moreover, PCSK9 inhibitors provide better adherence than statins and can help to improve compliance to statin treatment in a real-world setting [35]. Among 4015 post-MI patients, it was demonstrated that full adherence to treatment is associated with a lower rate of adverse cardiovascular events after 2-years follow-up, and reduction of annual direct medical costs for MI hospitalization [36].

### Study strengths and limitations

The presence of DLCN criteria, such as tendon xanthomas or corneal arches, and a family history of high cholesterol or vascular disease were not collected in our database. This information bias may result in an underestimation of the true prevalence of FH. However, the FH probability rate found in our population (approximately 3%) is consistent with other major studies [9, 14, 25, 32]. In addition, it is likely that many of the FH patients have been misclassified as having FH when in fact they are patients with a low FH probability. The use of a more refined method for FH diagnosis, such as the Dutch Lipid Clinic Network (DLCN) score, could improve the accuracy of FH diagnosis and management.

### Table 5 Logistic regression analysis to estimate multivessel disease

| Variable                        | Univariate OR (95% CI) P | Multivariate OR (95% CI) P |
|---------------------------------|--------------------------|---------------------------|
| Female (vs male)                | 0.878 (0.569–1.355) 0.557 | 0.661 (0.398–1.099) 0.110 |
| Age per y                       | 1.030 (1.012–1.048) 0.001 | 1.031 (1.010–1.052) 0.004 |
| Diabetes (vs no diabetes)       | 1.732 (0.996–3.011) 0.052 | 1.362 (0.737–2.516) 0.324 |
| Prior CAD                       | 1.546 (0.809–2.954) 0.187 | –                        |
| Chronic statins                 | 1.179 (0.726–1.914) 0.507 | –                        |
| FH (DLCN score ≥ 6 vs ≤ 2)      | 1.384 (1.108–1.730) 0.004 | 1.248 (0.881–1.766) 0.212 |
| LDL cholesterol. Per mg/dL      | 1.592 (1.113–2.278) 0.011 | 1.177 (0.672–2.059) 0.569 |
| CRP ≥ 3 mg/L (vs CRP < 3 mg/L)  | 2.428 (1.559–3.782) < 0.001 | 2.099 (1.326–3.323) 0.002 |

OR Odds ratio, CI confidence interval, FH familial hypercholesterolemia, DLCN Dutch Lipid Clinic Network, LDL Low density lipoprotein, CAD coronary artery disease, CRP C-Reactive Protein

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**Main results of the study**

- **Complex coronary lesions**
- **Bifurcation lesions**
- **Calcified plaques**
- **Multivessel disease**
- **Severe coronary artery disease**
- **High SYNTAX score**

**Fig. 4** Cartoon representation of the main results
patients in our study had tendon xanthoma. In 394 Japanese coronary patients undergoing PCI, most FH patients had Achilles heel xanthoma, which was predictive of the severity of coronary lesions [37]. Another recent series of 241 patients found that CAD patients had a high prevalence of Achilles heel xanthoma (18.2%), which was associated with multi-vessel coronary disease and imaging vulnerability criteria for atheromatous plaques [38]. Other missing data in our study include the statins doses, but we applied a correction factor of ≈30% to LDL-C levels in order not to overestimate the probability of FH. Moreover, genetic testing was not performed to confirm FH in the present study. In another recent study, a genetic diagnosis was obtained in 57 of 84 patients with LDL-C ≥6 (67.9%) [39]. However, the procedure used to calculate the probability of FH with the adapted Dutch lipid Clinic criteria is widely used in routine clinical practice.

Finally, the retrospective design of the study may potentially bias the results.

Conclusion
In patients with HF and acute MI, coronary lesions are anatomically complex, and characterized by multiple lesions, calcifications and bifurcation lesions. These features were associated with a high cholesterol burden and inflammation. The findings of this study reinforce the need for early screening for FH and highlight the fact that this condition is still under-treated. Aggressive cholesterol-lowering management is an important part of secondary prevention in these young high-risk patients.

Abbreviations
FH: Familial hypercholesterolemia; LDL-C: LDL-cholesterol; PCSK9: Proprotein convertase subtilisin/kexin type 9; DLCN: Dutch Lipid Clinic Network; CV: Cardiovascular; CAD: Coronary artery disease; MI: Myocardial infarction; RICO: Côte d’Or Myocardial Infarction Observatory; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft surgery; LVEF: Left ventricular ejection fraction; HF: Heart failure; CT: Computed tomography; ARS: Agence Régionale de Santé

Acknowledgements
We wish to thank Mrs. Suzanne Rankin for reviewing the English and Sylvie Mazencieux Agobert for editing assistance.

Authors’ contributions
Conceptualization: MF, YC and MZ; data curation: HY, FB and MM; formal analysis: MM and MZ; funding and acquisition: MZ and YC; methodology: YC and MZ; project administration, resources and supervision: LR; YC and MZ; resources: PB and DB; visualization: MF and MZ; writing original draft: HY and MZ; writing, review, and editing: all authors. All authors have read and agreed to the published version of the manuscript.

Funding
This work was supported by the Dijon-Bourgogne University Hospital, the Association de Cardiologie de Bourgogne, and by grants from the Agence Régionale de Santé (ARS) of Bourgogne Franche-Comté, and from the Regional Council of Bourgogne Franche-Comté.

Availability of data and materials
The data that support the findings of this study are available from Dijon-Bourgogne University Hospital. However, restrictions apply to the availability of these data, which were used under license for the current study and are thus not publicly available. Data can be made available from the authors upon reasonable request and with permission from the Dijon-Bourgogne University Hospital.

Declarations
Ethics approval and consent to participate
All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language.

Consent for publication
Not applicable.

Competing interests
MF reports having received grants, consulting fees and/or honoraria and delivering lectures for Abbott, Akcea/Ionis, Amgen, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Genzyme, Kowa, Merck and Co, Mylan, Pfizer, Sanofi/Regeneron and Servier. YC reports having received grants, consulting fees, honoraria and/or delivering lectures for Servier, Novartis, Boehringer, Pfizer, MSD, and Bayer. MZ received research grants from Amarin Corp. No conflict of interest to disclose for the other authors.

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Received: 4 March 2021 Accepted: 15 April 2021
Published online: 04 May 2021

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