Original Article

Montreal-FH-SCORE Predicts Coronary Artery Calcium Score in Patients With Familial Hypercholesterolemia

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is a monogenic disease characterized by a high concentration of low-density lipoprotein cholesterol. This population is considered to be at high cardiovascular risk; however, disease evolution remains heterogeneous among individuals. The coronary artery calcium (CAC) score is currently the best predictor of incidental major cardiovascular events in primary prevention in the general population. Few studies have described the CAC score in FH populations.

Methods: The objective of our study was to determine the predictors of the CAC score in FH patients. We retrospectively studied FH patients followed at the Montreal Clinical Research Institute (IRCM) Lipid Clinic.

Familial hypercholesterolemia (FH) is the most frequent autosomal codominant disorder of lipoprotein metabolism and is characterized by a marked elevation of low-density lipoprotein cholesterol (LDL-C). The prevalence of the disease is estimated to be approximately 1 in 200 to 1 in 250, but it can be even more elevated in specific population, such as the French-Canadian population, in which a genetic founder effect is present. FH is most often caused by mutations of the LDL receptor, but other mutations on apolipoprotein B (APOB) or proprotein convertase subtilisin/kexin type 9 (PCSK9) can be found.

The resulting lifelong exposure to high levels of LDL-C leads to an increased risk of premature cardiovascular disease (CVD). In hypercholesterolemic patients with similar LDL-C concentrations, the presence of an FH-causing mutation was associated with a 5-fold higher risk of CVD. However, there exists considerable variation in the rate of atherosclerosis progression and in the onset of CVD events in the FH population due to other genetic, clinical, and environmental factors. In fact, approximately 40% of untreated patients with familial hypercholesterolemia have a normal life span.

To better stratify the cardiovascular risk of FH patients, the Montreal-FH-SCORE (MFHS) was developed and validated in a retrospective cohort. The variables included in this score are age, sex, hypertension, high-density lipoprotein cholesterol, and smoking. Its predictive accuracy is elevated, with an area under the curve (AUC) of 0.84. MFHS could improve cardiovascular risk prediction beyond LDL-C in FH patients already on statin therapy. Therefore, MFHS may help clinicians to identify patients who need intensification of their treatment. The use of MFHS in the FH population is suggested by the latest Canadian Cardiovascular Society Position Statement.
who had a cardiac scan for CAC score, using the Agatston method, between 2013 and 2019.

**Results:** Final analysis included 62 FH patients. Mean age was 48 ± 14 years old, and 48% were men. Overall, 25 patients had a CAC score of 0 (40%), and 37 patients had a nonzero CAC score (60%). Sex, age, Montreal-FH-SCORE (MFHS), waist circumference, and statin exposure in years were significant predictors (P < 0.05) of a nonzero CAC score in a univariate model. MFHS was the only factor that remained significant in a multivariate model (odds ratio 1.34, 95% confidence interval 1.11–1.61, P = 0.002).

**Conclusions:** In conclusion, we found that MFHS, which includes traditional cardiovascular risk factors, was a predictor of a nonzero CAC score in FH patients. This finding suggests that MFHS may play a role in determining the cardiovascular risk and therefore the intensity of treatment in FH patients.

The coronary artery calcium (CAC) score, which is derived from non-enhanced cardiac computed tomography (CT), measures the accumulated burden of atherosclerosis and is significantly associated with medium- or long-term incidence of major cardiovascular events. It has been proven to be a better predictor of incident cardiovascular events than the traditional cardiovascular risk factors in the general population.12

A CAC score of zero is associated with a very low incidence of cardiovascular events, as demonstrated in a meta-analysis comprising large retrospective and prospective data.13 The American College of Cardiology/American Heart Association Task Force therefore recommends the use of the CAC score in intermediate-risk patients. Those individuals with a CAC score of zero may be reclassified as being at low cardiovascular risk, whereas those with a nonzero CAC score should be considered for statin therapy.14

CAC scores in FH patients are not often studied, as current guidelines do not recommend their use in populations considered to be at high risk of CVD. One study demonstrated a higher incidence of cardiovascular events in FH individuals with a nonzero CAC score, and an absence of cardiovascular events in individuals with a CAC score of zero.15

It is pertinent to determine if MFHS is a predictor of CAC score in FH patients in order to provide clinicians with a simple scoring system that could improve cardiovascular risk assessment in this population.

The objective of our study was therefore to establish the predictors of the CAC score in a cohort of FH patients.

**Methods**

**Study population**

The study population consisted of genetically confirmed FH patients followed at the Montreal Clinical Research Institute (IRCM) Lipid Clinic. All subjects presenting at the IRCM lipid clinic with an untreated LDL-C ≥5 mmol/L had a genetic screening for classic French Canadian mutations. These include the >15-kb deletion, >5-kb deletion, W87G (exon 3), E228K (exon 4), and C667Y (exon 14) in the low-density lipoprotein receptor (LDLR). When negative, subjects underwent a search for gene mutations by next-generation sequencing of LDLR, apolipoprotein B (APOB), low-density lipoprotein receptor adaptor protein 1 (LDLRAP1), or proprotein convertase subtilisin/kexin type 9 (PCSK9). Patients that were still negative were further investigated for mutations on the APOE, ARH, ABCG5, ABCG8, SORT1, and STAP1 genes at the Robarts Research Institute, Ontario, Canada. The study protocol was approved by the IRCM institutional review board and ethical committees; no informed consent was required.

**Assessment**

Baseline clinical information was obtained retrospectively using electronic medical records. Exposure to statins prior to obtaining the CAC score was measured in years to obtain statin-years. Diagnosis of diabetes and hypertension were made using the more recent Canadian clinical guidelines.16,17 Untreated lipid profile at baseline was defined as the first blood test done at IRCM and for which the patients underwent a 4-week washout of any lipid-lowering treatments. Lipid profile under treatment was defined as blood test done with statin treatment for at least 4 weeks. Lipid profiles were measured with standardized methods and in laboratories of the public health system. The Montreal-FH-SCORE (MFHS) was calculated for each patient by adding points for their age, their high-density lipoprotein cholesterol value, their sex, their smoking status, and the presence of hypertension.10

**CAC score**

Patients had a CT scan done between 2013 and 2019 for coronary calcium scoring assessment, at 1 of 2 centers offering
this test—University of Montreal Hospital Center and Montreal Heart Institute. This non–contrast enhanced cardiac scan was done using a Somatom Definition Flash 128-slice dual source CT (Siemens Medical Solutions, Forchheim, Germany). The thickness of the slices was 3 mm, and an axial reconstruction interval of 2.5 mm was made. Radiation dose for CT calcium scoring is approximately 1 mSv. Coronary calcium was quantified using the Agatston-Janowitz method based on the area and peak attenuation of coronary lesions with ≥130 Hounsfield units (HUs).

The CAC score was used as a continuous variable. CAC severity was expressed as a score of either zero or nonzero, as studied previously, and categorized as 0, 0 to 100, or >100, as presented in the American College of Cardiology/American Heart Association Task Force guidelines for the general population in primary prevention. A CAC score >100 was also considered a marker of severe disease in the European guidelines on cardiovascular disease prevention in clinical practice. For coronary artery assessment, the coronary segments were defined in terms of the 1999 American Heart Association classification. All segments were included. Multivessel disease was defined as coronary calcification present on the 3 major coronary arteries, namely the left anterior descending, the circumflex, and the right coronary artery.

Statistical analysis

Normality was assessed using skewness and kurtosis between −1 and 1. Continuous variables were expressed as mean ± standard deviation (SD) for variables with a normal distribution or median and interquartile range for variables with an abnormal distribution. Other categorical variables were expressed in frequency (n [%]).

To improve data distribution, systolic blood pressure, triglycerides, and lipoprotein (a) were transformed using a logarithm. As CAC scores were not distributed normally, results were transformed using log (CAC score +1), which displays a normal distribution. Logistic regression models were used to assess the univariate and multivariate predictors of a nonzero CAC score.

MFHS median was used to create 2 groups. Logistic regression models were used to compare prevalence of nonzero CAC score, CAC score >100, and multivessel disease. Student t tests were used to compare MFHS between patients with a zero CAC score and a nonzero CAC score. The χ² test was performed to compare the prevalence of nonzero CAC scores in each MFHS group. ROC curves were generated to compare MFHS with a score that only combines age and sex.

Statistical analyses were performed using SPSS 25.0 (IBM Corp, Armonk, New York). A P value <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

We identified patients followed at our clinic who had a CT scan for CAC score done between 2013 and 2019 and presented a genetic diagnosis of FH. The study population included 62 FH patients; 61 patients were heterozygous, and one was compound heterozygous with a mutation on each allele. The >15-kb deletion was the most frequently observed mutation (47%). One patient presented a mutation on APOB, but all the others had mutations on the LDLR.

The clinical characteristics of the patients are shown in Table 1. At the time of the CT scan, patients had a mean age of 48 ± 14 years, and 30 patients were male (48%). All patients in the study had a history of statin exposure and were being treated with statins. Statin exposure before CAC score measurement was 11 ± 9 years. Mean untreated LDL-C was 6.21 ± 1.78 mmol/L, and LDL-C undertreatment was 3.33 ± 1.04 mmol/L. This value represents a mean change of 44.04% ± 23.32%. No patient had a history of CVD at baseline, and therefore all patients were considered in primary prevention.

CAC score

Among the 62 FH patients, 25 (40%) had a CAC score of 0, whereas 13 had a CAC score between 1 and 100 (21%), and 24 had a CAC score >100 (39%).

Predictors of CAC score in FH patients

The predictors of a nonzero CAC score were sex (odds ratio [OR] 4.22, 95% confidence interval [CI] 1.41–12.65, P = 0.01), age (OR 1.11, 95% CI 1.05–1.17, P = 0.0003), MFHS (OR 1.27, 95% CI 1.13–1.43, P < 0.0001), waist circumference (OR 1.08, 95% CI 1.00–1.16, P = 0.04), and statin exposure before CAC (OR 1.08, 95% CI 1.01–1.15, P = 0.03; Table 2). In a multivariate model including statin exposure and waist circumference, the MFHS was the only

Table 1. Subjects’ characteristics

| Variables                | Reference | Monogenic FH (N = 62) |
|--------------------------|-----------|-----------------------|
| Male sex                 | 30 (48)   | 30 (48)               |
| Age at time of CAC, y    | 48 ± 14   | 48 ± 14               |
| Hypertension             | 4 (6)     | 4 (6)                 |
| SBP, mm Hg               | 114 (107-124) | 114 (107-124)       |
| DBP, mm Hg               | 71 ± 10   | 71 ± 10               |
| Smoking                  | 40 (65)   | 40 (65)               |
| Never                    | 14 (23)   | 14 (23)               |
| Past Current             | 8 (13)    | 8 (13)                |
| Diabetes                 | 4 of 61 (7) | 4 of 61 (7)         |
| Montreal-FH-SCORE       | 22 ± 8    | 22 ± 8                |
| BMI, kg/m²               | 25.6 ± 4.5 | 25.6 ± 4.5           |
| Waist circumference, cm  | 88.4 ± 10.4 | 88.4 ± 10.4         |
| Type of mutation—null    | 29 of 46 (63) | 29 of 46 (63)      |
| Statin exposition before CAC, y | 11 ± 9 | 11 ± 9               |
| Total cholesterol, mmol/L | 8.45 ± 2.15 | 8.45 ± 2.15         |
| Triglycerides, mmol/L    | 1.04 (0.90-1.71) | 1.04 (0.90-1.71)   |
| Untreated LDL-C, mmol/L  | 6.21 ± 1.78 | 6.21 ± 1.78         |
| Treated LDL-C, mmol/L    | 3.33 ± 1.04 | 3.33 ± 1.04         |
| Change in LDL-C, %       | −44.04 ± 33.32 | −44.04 ± 33.32   |
| HDL-C, mmol/L            | 1.38 ± 0.48 | 1.38 ± 0.48         |
| Non-HDL-C, mmol/L        | 7.03 ± 2.17 | 7.03 ± 2.17         |
| Apolipoprotein B, g/L    | 1.70 ± 0.51 | 1.70 ± 0.51         |
| Lipoprotein (a), g/L     | 0.26 (0.10-0.68) | 0.26 (0.10-0.68) |
with a MFHS below 24 (87% vs 30%, OR 15.8, 95% CI 4.3
24, the prevalence of nonzero CAC scores was higher in
respectively), as well as the prevalence of multivessel disease
(Table 3).

| predictor that remained statistically significant (OR 1.34, 95% CI 1.11–1.61, P = 0.002; Table 3). Supplemental Figure S1 represented receiver operating curves (ROC) curves comparing MFHS with a version of the score that was combining points for age and sex only. The area under the curve (AUC) for the MFHS (0.865) was better than the AUC for the score that combines age and sex (0.824). However, this difference did not reach statistical significance (P = 0.21).

The median of MFHS among the studied population was 24. The prevalence of nonzero CAC scores was higher in patients with a MFHS of 24 or more compared to patients with a MFHS below 24 (87% vs 30%, OR 15.8, 95% CI 4.3–58.3, P < 0.001, respectively). The proportion of CAC scores above 100 was also higher in patients with a MFHS of 24 or more compared to patients with a MFHS below 24 (87% vs 30%, OR 15.8, 95% CI 4.3–58.3, P < 0.0001, respectively), as well as the prevalence of multivessel disease (48% vs 10%, OR 8.4, 95% CI 2.1–33.7, P = 0.003, respectively; Supplemental Figure S2).

Median MFHS in 25 patients with a zero CAC score was 16 (Q1-Q3; 12–22.5), and median MFHS in 37 patients with nonzero CAC score was 26.5 (21.75–31.75; P < 0.0001; Fig. 1). The majority of patients (15 of 18) with a MFHS of 17 or less had a CAC score of 0, and all the patients with a MFHS higher than 28 had a nonzero CAC score (Fig. 2). Figure 3 displays prevalence of nonzero CAC score in 3 groups of MFHS (17% in MFHS 17 or less; 67% in MFHS 18 to 28; and 100% in MFHS more than 28, P < 0.0001).

### Discussion

The CAC score is well validated as a marker of cardiovascular risk in the general population, but it has been less studied in FH patients.

In this cohort, 40% of FH patients presented with a CAC score of 0, which is comparable to percentages in recent published FH cohorts (51%22 and 49%17). However, other studies in FH patients have shown a lower prevalence of a CAC score of 0 (21%23 and 26.6%24). This discrepancy is probably due to a difference in the mean age of patients among these FH cohorts. A CAC score of 0 does not exclude the presence of atherosclerosis, but a previous study established that only 4% of FH patients with a CAC score of 0 had a noncalcified plaque, which in all cases occluded less than 50% of the lumen.23

Miname et al. studied the predictive value of CAC for incidence of major atherosclerotic cardiovascular events in a prospective cohort of 206 patients.15 The authors found that CAC score was an independent predictor of incident major atherosclerotic cardiovascular events. No events were reported in patients with a CAC score of 0 over a median period of follow-up of 3.7 years. For patients with CAC scores between 1 and 100, the annual rate of events for 100 patients was 26.4%, and 44.1% for a CAC score >100.

As in the general population, male sex and age, 2 major traditional cardiovascular risk factors, were predictors of a nonzero CAC score in this FH cohort.7 Another predictor of a nonzero CAC score was waist circumference. Indeed, an elevated waist circumference is part of the metabolic syndrome, which is associated with an increase in atherosclerotic disease.12

In this study, exposure to statins was a predictor of a nonzero CAC score. This result is consistent with the concept of a “statin paradox” that has been previously described. In fact, high-dose and long-term statin therapy increase coronary artery calcifications.29 However, this increase in calcification is associated with an overall plaque regression, suggesting that it may be a reflection of plaque repair rather than plaque progression.30 Statin exposure may also be a marker of disease severity, as patients with higher cardiovascular risk will be treated more aggressively and rapidly. The fact that all patients in this study were treated with statins does not represent a limitation. The study by Miname et al. that looked at prospective cardiovascular events in FH patients had 68.9% patients treated with statins at baseline, and 96.6% at follow-up, and they still observed an association between CAC score and incident cardiovascular events.15 It is interesting to note that LDL-C (at baseline or treated) was not a predictor of abnormal CAC score in the present cohort.

Finally, MFHS was a strong predictor of a nonzero CAC score. Two of its components, age and sex, were also significant predictors in univariate analysis. In a multivariate model including waist circumference and years of exposure to statins,
the MFHS was the only one to remain statistically significant. The MFHS ROC curve did not show a statistically higher AUC than a version of the score that combined only age and sex. This could be the result of a lack of power, as this analysis was significant in the original MFHS publication comprising 725 FH patients.10

In the original article that first describes the MFHS, the group with MFHS above the median of 21 had a 10-fold increase in the prevalence of cardiovascular disease.10 The MFHS median of 24 in the present FH cohort is consistent with the original study. Significant differences in the proportion of nonzero CAC score, CAC score >100, and multivessel coronary calcifications were found when comparing the 2 groups along the median.

An MFHS score less than 18 seems to be predictive of a CAC score of 0, and an MFHS above 28 appears to be predictive of a nonzero CAC score. An MFHS between 18 and 27 displays more variability regarding prediction of CAC score and can be considered a grey zone.

As all patients with a MFHS higher than 28 had a nonzero CAC score, we could consider not assessing CAC score in this group. For patients in the grey zone of MFHS, 67% have a nonzero CAC score and could be reclassified at very high cardiovascular risk, and 33% would remain at usual high risk for FH patients.

In FH patients, the treatment approach has always put emphasis on the LDL-C target. However, the extent of atherosclerosis and the age at first cardiovascular event remain heterogeneous among individuals. Statin therapy has reduced the severity and age of onset of cardiovascular events.6 The Framingham Risk Score cannot be used in this population as it was not created to assess cardiovascular risk in FH patients. On the contrary, the MFHS has been developed and validated with FH patients, and our study demonstrates its correlation with the CAC score. Our results suggest that the MFHS may be useful as a predictor of subclinical atherosclerosis. Hence, an MFHS result higher than 28 would lead to a treatment intensification that implies targeting an LDL-C level lower than 2.00 mmol/L (beyond the 50% reduction) and would necessitate the addition of a PCSK9 inhibitor in most cases. FH patients with an intermediate MFHS result (18–28) would benefit from a CAC score to reclassify their risk.

Our study also reinforces the importance of managing other cardiovascular risk factors as part of the treatment, such as control of blood pressure, smoking cessation, and weight loss.

Possible limitations of this study include its retrospective design and the relatively small sample size. However, all included FH patients had a genetic diagnosis and were not selected using a purely clinical diagnosis such as scoring systems (Dutch Lipid, Simon Broome). The presence of a documented FH-causing mutation in all patients eliminated the risk of misdiagnosis. Another limitation is the absence of evaluation of soft plaques on coronary arteries with a CT coronary angiogram. However, the CAC score is a simple exam that is well validated in the general population for cardiovascular risk assessment and has been recently studied in FH patients, whereas CT coronary angiogram is a more invasive and expansive exam. Exposure to statins was quantified retrospectively, and duration of treatment preceding the referral to our center was self-reported by patients. Therefore,
stain exposure was rounded to years. Also, the dosage of the statins received and the compliance to treatment was not always available, which led to a less-precise evaluation of true exposure. Another limitation to the study is the absence of evaluation of the impact of environmental factors other than smoking on MFHS, as they were not consistently documented in the charts. As the CAC score is not routinely assessed in FH patients, this cohort may represent a different subgroup of FH patients, which may have introduced a selection bias. Also, the MFHS has been retrospectively validated, and therefore it can assess CVD prevalence but not incidence. Finally, this study was not evaluating clinical outcomes, and results of MFHS obtained could not be used to predict clinical outcomes based on this study.

**Conclusion**

This retrospective study demonstrates that traditional cardiovascular risk factors, combined in the MFHS, were predictors of a nonzero CAC score in FH patients. This suggests that the MFHS could be used as a tool in the prediction of CVD risk, helping clinicians to modulate the intensity of treatment in FH patients. A prospective study is currently underway to evaluate the predictive value of MFHS for incident cardiovascular events.

**Acknowledgements**

The authors thank the Montreal Clinical Research Institute (IRCM) Lipic Clinic research team and the nursing staff for their everyday help, support, and implication.

S.B. had full access to all the data and takes primary responsibility for the final content.

**Funding Sources**

The authors have no funding sources to declare.

**Disclosures**

A.B. received research grants from Akcea, Amgen, Astra Zeneca, the Fondation Leducq, Merck Frosst, and Sanofi. He has participated in clinical research protocols from Acasti Pharma Inc, Akcea, Amgen, Astra Zeneca, Ionis Pharmaceuticals, Inc, The Medicines Company, Merck Frosst, Novartis, Pfizer, Regeneron Pharmaceuticals Inc, and Sanofi. He has served on advisory boards and received honoraria for symposia from Akcea, Amgen, and Sanofi.

S.B. has participated in clinical research protocols from Akcea, Amgen, The Medicines Company, and Sanofi. She has served on advisory boards for Akcea, Amgen, Eli Lilly, Merck Frosst, Novo Nordisk, Sanofi, and Valeant Pharmaceuticals, and received honoraria for symposia from Akcea, Amgen, Boehringer Ingelheim, Merck Frosst, Novo Nordisk, and Sanofi-Aventis.

S.B.-B., M.P., M.F., L.B., and N. S-P. have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.09.007.