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Original Article

Cardiovascular disease in familial hypercholesterolemia: Validation and refinement of the Montreal-FH-SCORE

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BACKGROUND: Familial hypercholesterolemia (FH) is a disease characterized by increased low-density lipoprotein cholesterol and premature cardiovascular disease (CVD) but there is marked individuality in the occurrence of CVD events. Recently, the Montreal-FH-SCORE (MFHS) has been shown to stratify CVD frequency in FH subjects, but this score has not yet been validated.

OBJECTIVE: The aims of the present study were to conduct an independent external validation of the MFHS in a retrospective cohort of heterozygous FH and to identify additional variables that could significantly improve the prediction of prevalent CVD.

METHODS: The MFHS calculation is based on 5 variables: age, high-density lipoprotein cholesterol, gender, hypertension, and smoking status. This score was validated in a cohort of 718 adult FH using receiver operating characteristic (ROC) curves analysis to determine the discriminatory ability of the MFHS. The performance of the MFHS was compared to a novel Combined-FH-SCORE in 1388 FH.

RESULTS: The MFHS had an excellent discrimination for prevalent CVD events in the validation cohort, with an area under the receiver operating characteristic curve of 0.799 (0.766–0.832, $P < .0001$). Patients with a high MFHS score presented a significant 8.8-fold increased odd of CVD events compared with patients with a low score (95% confidence interval 5.8–13.3, $P < .0001$). The addition of lipoprotein(a) to the score did not improve the prediction of CVD events (area under the receiver operating characteristic curve 0.823 vs 0.817, $P = .11$).

CONCLUSION: This study confirmed that the MFHS is a strong predictor of prevalent CVD in FH and that the addition of lipoprotein(a) offers a minor improvement in the discrimination of the score.

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Introduction

Familial hypercholesterolemia (FH) is the most prevalent autosomal co-dominant genetic disease worldwide with an estimated frequency of 1:250 to 1:500.[1–3] This disease is mainly caused by mutations in low-density lipoprotein (LDL) receptor (*LDLR*), apolipoprotein B (*ApoB*), or proprotein convertase subtilisin/kexin-type 9 genes. Typically, FH leads to extremely high plasma LDL cholesterol (LDL-C) concentrations and high lifetime risk of cardiovascular disease (CVD). Indeed, coronary symptoms will be present in 45% of men and 20% of women with heterozygous FH (referred as FH in this article) before the age of 50 years.[4] Annually, it has been estimated that 5% of myocardial infarctions before age of 60 years and 20% before age of 45 years occur in FH patients.[5] However, CVD risk in FH is variable and circulating LDL-C level is not the sole indicator for risk prediction.[3,6–11] CVD risk assessment and intensive risk factors management in FH should therefore be the cornerstone of cardiovascular prevention. The current established cardiovascular risk estimators such as the Framingham Risk Score, the Pooled Cohort Equation, and the European SCORE were created to assess CVD risk in the general population and cannot be applied to FH subjects.[12] The recently developed Montreal-FH-SCORE (MFHS)[13] represents the first scoring tool used to stratify CVD prevalence in FH subjects. This point scoring system uses 5 variables, namely age, high-density lipoprotein cholesterol (HDL-C), gender, hypertension, and smoking. The MFHS showed an excellent association with prevalent CVD with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.84 in the development cohort of 670 French Canadian adult FH. However, the MFHS has never been validated in an external cohort of FH patients.

The objectives of this study were to conduct an independent validation of the MFHS to test its association with CVD and to use the combined data from both cohorts to determine if other variables can significantly improve the prediction of prevalent CVD.

Material and methods

Study population and data collection

Validation cohort

All data of the validation cohort came from patients screened for FH at the Chicoutimi Hospital Lipid Clinic or at ECOGENE-21 Clinical Research Center (Saguenay, Québec, Canada) between 1993 and 2014. A total of 718 FH adult (aged ≥18 years) patients were included in the cohort. All these confirmed FH patients carried a classical French Canadian mutation in the *LDLR* gene, including deletion (del) > 15kb of the promoter and exon 1, del > 5 kb of exons 2 and 3, W66G (exon 3), E207K (exon 4), Y468X (exon 10), C646Y (exon 14), and R329X (exon 7). Demographic and clinical characteristics of subjects such as gender, age, hypertension, diabetes, smoking, body mass index, CVD events, medical history, and lipid profile were collected at the screening visit by trained nurses or physicians. The data collection process has been described elsewhere.[14] CVD events included angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or ischemic cerebrovascular accident. Hypertension was diagnosed using the Canadian Hypertension Education Program criteria. The diagnosis of diabetes was made according to the Canadian Diabetes Association guidelines. The most recent version of these criteria that was available at the time of patient evaluation was used. Information about retrospective CVD events was self-reported by the patients at the time of their first consultation at the lipid clinic. Documentation concerning these events was obtained by requesting copies of relevant tests (eg, coronarography, stress test, and so on) and hospital visits. A written informed consent, approved by the Chicoutimi Hospital Ethics Committee in accordance with the Declaration of Helsinki, was obtained from all patients before to proceed to the genetic testing.

Combined cohort

The combined cohort consists of the combination of the development cohort (Patients from the Montreal Clinical Research Institute (n = 670)) and the validation cohort (n = 718). A total of 1388 adult FH patients were included in the combined cohort. The details of this development cohort have been previously reported in the original publication of the MFHS.[13]

Biochemical analyses

Most patients in the validation cohort (n = 624) followed a 2- to 4-week washout of any lipid-lowering medication before the blood sampling. In this group, LDL-C was calculated using the Friedewald formula. A validated equation was used to calculate the untreated LDL-C value in patients who did not stop their lipid-lowering medication (n = 94) at the time of screening.[8] In the validation cohort, the method used to measure the 12-hour fasting lipid profile has previously been published elsewhere.[14] In the development cohort, the LDL-C was measured using the reference method.[15] Lipoprotein(a) [Lp(a)] concentration was measured using a commercial ELISA kit (Macra EIA Kit; Strategic Diagnostics Industries, Inc, Newark). Method for biochemical analysis in the development cohort is described in Paquette et al. 2017.[13] All biochemical analyses were done in core laboratories of the public health system.

DNA analyses

In the validation cohort, DNA samples were extracted from whole blood using the Gentra Puregene Blood Kit (Qiagen Inc, Valencia, CA). Identification of the *LDLR*