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RESEARCH LETTER

Predicting High-Risk Plaques in Familial Hypercholesterolemia Using Clinical Variables and Coronary Artery Calcium

Familial hypercholesterolemia (FH) is a disorder associated with accelerated atherosclerotic cardiovascular disease (ASCVD). Because ASCVD varies among affected individuals, risk prediction tools specific to FH exist.[1] These are, however, cohort based and may underestimate risk in individuals. Therefore, there is an unmet need for a more precise risk prediction in patients with FH.

Coronary artery calcium (CAC) scoring has been proposed for individualized risk assessment in FH, but it is unable to assess noncalcified plaques. This is especially relevant to FH patients who develop ASCVD prematurely and may exhibit high-risk plaques (HRPs) without calcification. Coronary computed tomographic angiography (CCTA) allows for the identification of HRPs. Studies in the non-FH population have demonstrated the presence of HRPs is predictive of ASCVD events.[2] Early work has demonstrated similar benefits in the FH population.[3] However, CCTA adds costs and exposes patients to greater radiation and intravenous contrast. We aimed to develop a model to predict the presence of HRPs using clinical variables and CAC scoring in FH.

We recruited patients from a specialized lipid service in Perth, Western Australia, Australia, with a Dutch Lipid Clinic Network Score ≥5. Indications for CAC score and CCTA being performed were symptoms of coronary artery disease, peripheral artery disease, cerebrovascular disease, and the presence of multiple risk factors.[4] Patients were consented at consultation, and clinical and imaging characteristics were recorded. The 10-year SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) risk score was calculated for each participant, a risk algorithm specific to FH.[1] All variables were available to calculate SAFEHEART risk, except body mass index, which was not available in 22 cases.

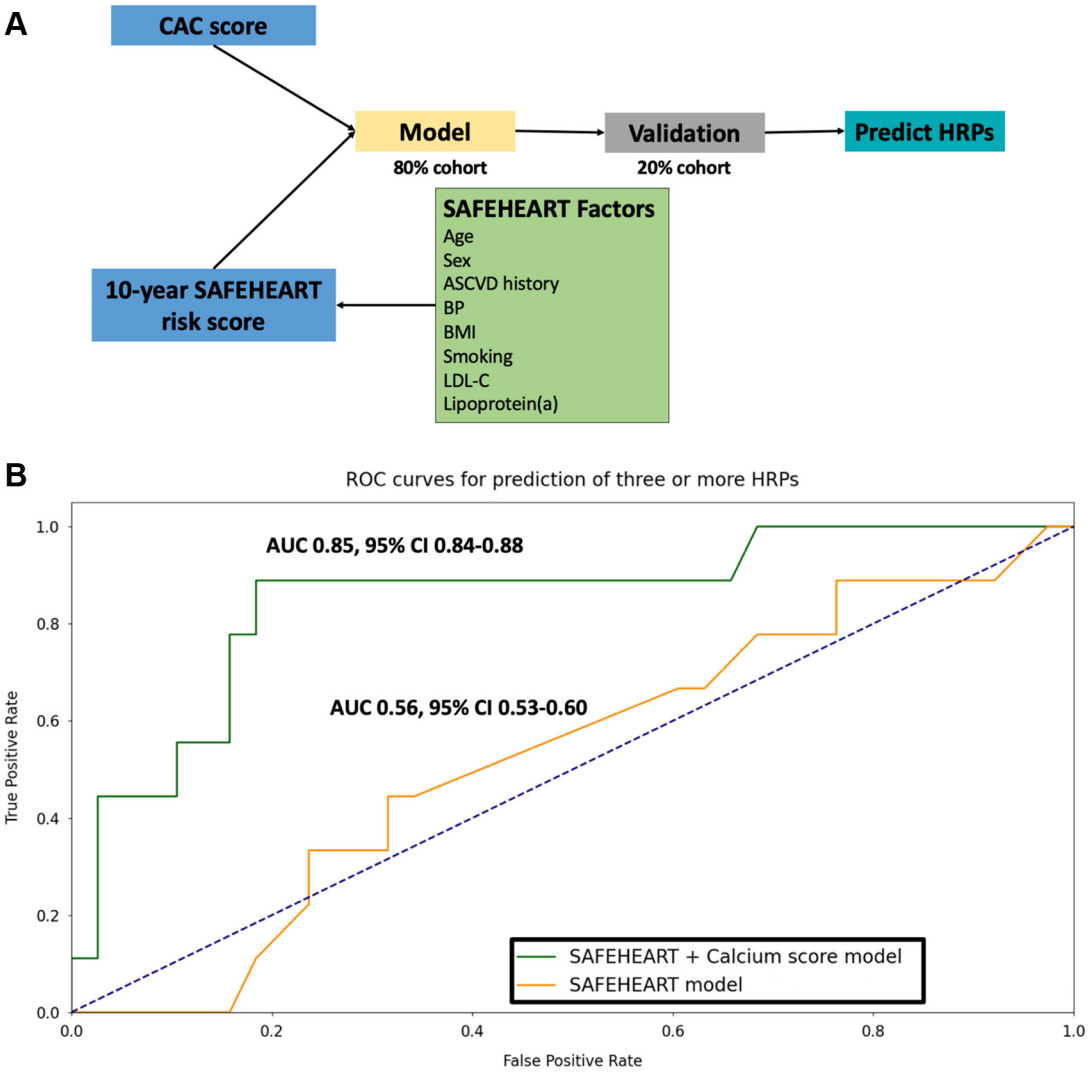
CCTA scans were analyzed with semiautomated software (Q AngioCT Research Edition, Medis Medical Imaging Systems) by a reader blinded to patient characteristics. Analysis of the major coronary arteries was performed, and coronary segments were evaluated for HRPs, including positive remodeling, low-attenuation plaque, and spotty calcification. HRPs were recorded as the presence of at least 2 HRPs within the same segment. We focused on individuals with ≥3 segments with HRPs; we previously demonstrated that ≥3 segments with HRPs predicted ASCVD events in FH.[3] This study was approved by local ethics institutions.

Logistic regression models were developed to predict HRPs (**Figure 1**). The first model was based on the SAFEHEART risk score, and the second model added CAC score to the SAFEHEART risk score. The coefficient of each variable was iteratively optimized using large-scale bound-constrained optimization algorithm. Data from 80% of the cohort were used to develop the models, which were then validated with the remaining 20%. The process was repeated 50 times, with nonoverlapping data between training and test cohorts. The area under the curve (AUC) was measured with each evaluation, and the mean AUC and 95% CI were calculated. Modeling and statistical calculations were performed using scikit-learn and Scipy with Python 3.7.

A total of 233 individuals were included; the mean age was 54 ± 11.9 years, 42.9% were male, the mean Dutch Lipid Clinic Network Score was 9.4 ± 4.3, 49.8% had an FH mutation, the mean plasma low-density lipoprotein cholesterol concentration was 170.2 ± 69.06 mg/dL, 66.1% were on lipid lowering therapy, 63.5% had CAC present, and 14.2% had ≥3 HRPs. HRPs were present in 20% of individuals without CAC, with 2.4% demonstrating ≥3 HRPs. The diagnostic validity of the SAFEHEART model for predicting the presence of ≥3 segments with HRPs was modest, with an AUC of 0.56 (95% CI: 0.53-0.60). Integrating both SAFEHEART and CAC score improved the model, with an AUC of 0.85 (95% CI: 0.84-0.88) compared with using SAFEHEART score alone ($P < 0.001$). The model performance remained similar in patients aged <45 years and when mutation status was considered.

This is the first study to investigate a model for predicting HRPs using CAC score and clinical characteristics in an FH population. Using such models

FIGURE 1 Predictive Models Development and Performance



(A) Model generation and validation. **(B)** Area under the receiver operating characteristic (ROC AUC) curves of predictive models for high-risk plaques (HRPs) (≥3), between models $P < 0.001$. ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; BMI = body mass index; CAC = coronary artery calcium; LDL-C = low-density lipoprotein cholesterol; SAFEHEART = Spanish Familial Hypercholesterolemia Cohort Study.

allows for more personalized ASCVD risk prediction. The benefits of incorporating CCTA including assessment of HRPs to guide treatment have been established in the non-FH population; these benefits would potentially be greatest in FH.[5] Our results demonstrated that a model based on the SAFEHEART and CAC score can accurately predict HRPs. In contrast, a model based on the SAFEHEART model alone poorly predicted HRPs, which may indicate that HRPs capture an at-risk population not identified by the SAFEHEART score. With the addition of CAC to the SAFEHEART score, there was incremental gain in the accuracy of prediction of HRPs, highlighting the value of CAC in risk stratification. However, CAC represents a late stage in atherosclerosis and may be absent in younger individuals that still may have noncalcified HRPs; therefore, a model merging CAC score with SAFEHEART risk score may be advantageous. The use of such a model reveals individuals at risk who may benefit from intensified treatment and may engage patients to be more involved in treatment decisions.

In conclusion, we developed a model to predict the presence of HRPs in FH. Incorporation of such a model into clinical practice may enhance cardiovascular risk prediction and therapy. Further studies with larger populations and outcome data are still needed before integration into routine clinical care.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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