



Subclinical coronary atherosclerosis and cardiovascular risk stratification in heterozygous familial hypercholesterolemia patients undergoing statin treatment

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Purpose of review

To discuss the heterogeneity of atherosclerotic cardiovascular disease (ASCVD) risk in heterozygous familial hypercholesterolemia and evidence and limitations of clinical risk scores and subclinical coronary atherosclerosis (SCA) imaging to evaluate risk.

Recent findings

Risk evaluation in contemporary familial hypercholesterolemia cohorts needs to consider the cause of the familial hypercholesterolemia phenotype, for example the presence of autosomal molecular defects that impart a greater ASCVD risk than in polygenic hypercholesterolemia, prospective follow-up and the impact of statin treatment. As atherosclerosis is multifactorial, clinical scores like the Montreal familial hypercholesterolemia score and SAFEHEART risk equation have been proposed to stratify ASCVD in statin-treated, molecularly defined familial hypercholesterolemia individuals. However, these scores need further validation. SCA distribution in familial hypercholesterolemia individuals undergoing conventional lipid-lowering treatment is heterogeneous, with 45–50% of individuals not presenting any coronary artery calcification (CAC). One study suggests that the absence of CAC associates with no ASCVD events in asymptomatic familial hypercholesterolemia individuals undergoing statin therapy despite elevated residual LDL-cholesterol levels. In contrast, the presence of CAC was independently associated with ASCVD events.

Summary

ASCVD risk is heterogeneous in statin-treated familial hypercholesterolemia individuals. Further studies are necessary to determine how risk stratification, especially with SCA detection, impacts on prescription of proprotein convertase subtilisin kexin type 9 inhibitors within a cost-constrained environment.

Keywords

coronary artery calcification, familial hypercholesterolemia, proprotein convertase subtilisin kexin type 9, risk stratification, statins, subclinical atherosclerosis

INTRODUCTION

Familial hypercholesterolemia is an autosomal codominant disorder of LDL catabolism affecting 1/250–1/500 people in different countries of the world [1–3]. Heterozygous familial hypercholesterolemia is associated with a two-fold to three-fold greater risk of coronary artery disease (CAD) when compared to unaffected individuals [1]. This risk is more pronounced in individuals 20–40 years old [4**] and the clinical course of CAD in familial hypercholesterolemia is variable [5–7], as the disease course is driven not only by elevated LDL-C burden but also by the presence of other classical atherosclerotic cardiovascular disease (ASCVD) risk

biomarkers [5,7–10]. Observational studies have shown that lipid-lowering therapy, particularly with

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KEY POINTS

- Risk of ASCVD is heterogeneous among heterozygous familial hypercholesterolemia individuals.
- Risk evaluation on contemporary familial hypercholesterolemia populations must consider the presence of an autosomal molecular defect, prospective follow-up and previous use of statins.
- Clinical risk evaluation scores like Montreal risk score and SAFEHART risk equation are promising but need further evaluation.
- SCA, mainly CAC, is heterogeneous in familial hypercholesterolemia individuals undergoing statin treatment (i.e. it is absent in 45–50% of patients).
- In one study, CAC was independently associated with ASCVD events in individuals undergoing statin therapy, whereas its absence may indicate a lower risk familial hypercholesterolemia population in the intermediate term.

statins, reduces the risk of clinical events in familial hypercholesterolemia individuals. Thus, it is currently recommended that the latter must be instituted as early as possible to reduce ASCVD events [4^{11,12}]. However, while many individuals persist with elevated residual morbidity and mortality risk despite optimal treatment, others remain event free even during long-term follow-up [4^{11,12}].

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors are a new class of LDL-C reducing agents which are extremely efficacious in reducing residual elevated LDL-C in heterozygous familial hypercholesterolemia. In addition, recent evidence also suggests that these medications reduce ASCVD disease in familial hypercholesterolemia individuals [13¹³]. Unfortunately, access to PCSK9 inhibitors is restricted by their elevated costs and lack of reimbursement, and overall low value from a societal cost perspective [14]. Therefore, a strategy based on risk stratification to identify higher residual ASCVD risk in familial hypercholesterolemia individuals may improve cost-effectiveness of this treatment on top of mandatory statin and ezetimibe treatment in a healthcare environment with limited resources.

The recently published guidelines from the American College of Cardiology/American Heart Association have recognized that detection of coronary artery calcification (CAC) by cardiac computed tomography imaging helps reclassify ASCVD risk in the general population [15]. CAC is a surrogate of atherosclerotic plaque burden and is an independent marker of clinical events in the general population [16] as well as in higher risk individuals such

as diabetic patients [17]. Previously, the International Atherosclerosis Society recommended the use of CT coronary imaging to improve risk stratification in familial hypercholesterolemia; however, this recommendation was based on circumstantial evidence from cross-sectional and retrospective data in familial hypercholesterolemia as well as extrapolation from prospective studies done in the general population [6].

In the present article, we update information on the possible role and limitations of both clinical risk evaluation and SCA detection for risk stratification in the primary prevention setting for heterozygous familial hypercholesterolemia individuals undergoing standard lipid-lowering therapy.

HETEROGENEOUS ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK IN FAMILIAL HYPERCHOLESTEROLEMIA INDIVIDUALS ON STATIN ERA

In a large prospective study, Mundal *et al.* [18¹⁸] evaluated the risk of acute myocardial infarction (AMI) in 2795 individuals undergoing statin therapy at baseline, in comparison to those from general population, who were all followed from 2001 to 2009 [16]. The authors found that the highest relative risk of AMI occurs between ages 25 and 39 years with a trend to decrease with aging. Similar findings were demonstrated in the 26-year follow-up of the Simon Broome Registry. In this study, statin treatment reduced CHD mortality though it persisted to be relatively elevated in the 20–39 year age stratum and in women despite treatment [4¹⁸]. This shows that some familial hypercholesterolemia individuals will suffer a premature ASCVD event, whereas others will survive event free. Yet, it remains unknown how much of this tendency is influenced by genetics and associated with very high LDL-C vs. the presence of other risk factors, the individual's susceptibility to atherosclerosis or inadequate statin treatment [4^{18,8}].

VALUE AND LIMITATIONS OF CLINICAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK STRATIFICATION IN FAMILIAL HYPERCHOLESTEROLEMIA IN THE STATIN ERA

Classical ASCVD risk biomarkers, other than higher LDL-C burden, have been associated with vascular events in familial hypercholesterolemia individuals [5,7–9,19]. Cross-sectional and retrospective studies have shown an association of older age, male sex, hypertension, low HDL-C levels, higher lipoprotein(a) [Lp(a)] blood concentrations and

smoking with previous ASCVD occurrence in familial hypercholesterolemia individuals [8,9,19]. These studies, however, had some caveats: lack of prospective design; absence of molecular diagnosis in all enrolled individuals and therefore inclusion of lower risk polygenic hypercholesterolemia individuals with an familial hypercholesterolemia-like phenotype instead of true higher risk familial hypercholesterolemia individuals [4²²,20,21]; and inclusion of many individuals who are not undergoing statin treatment, an intervention known to change the natural history of ASCVD.

Risk stratification studies of contemporary familial hypercholesterolemia cohorts must therefore consider prospective design, molecular diagnosis and the risk mitigating effects of previous statin treatment on ASCVD. Indeed, recently, the Montreal familial hypercholesterolemia risk score [7] and the Spanish SAFEHEART risk equation (SAFEHEART-RE) [5] considered some of these parameters in their design.

Paquette *et al.* [7] retrospectively evaluated 670 molecularly proven Canadian individuals with familial hypercholesterolemia who were undergoing statin therapy. In their study, older age, male sex, hypertension and smoking were independently associated with ASCVD prevalence. More recently, the authors validated their risk equation in another molecularly characterized Canadian familial hypercholesterolemia population with 718 individuals with good statistical discrimination [22]. However, these studies were still limited by their retrospective design and relatively small number of clinical events. Perez de Isla *et al.* [5] evaluated 2404 molecularly proven familial hypercholesterolemia individuals, 84% using statin at baseline who were followed for 5.5 ± 3.2 years in the Spanish Familial Hypercholesterolemia Registry (SAFEHEART). In addition to the risk markers defined by the Canadian study, previous ASCVD event history, elevated BMI (more than 30 kg/m^2), high residual LDL-cholesterol (> 100 or $> 160 \text{ mg/dl}$) and Lp(a) levels more than 50 mg/dl were independently associated with ASCVD onset or recurrence. Using these parameters, the SAFEHEART-RE had good discrimination (C index 0.85 overall, 0.81 for primary prevention) with excellent calibration for both primary and secondary prevention. However, the SAFEHEART-RE was still limited by the relatively small number of events (5.6%), a possible confounding by statin treatment and relatively short-term follow-up. Finally, similar to the Montreal familial hypercholesterolemia score, SAFEHEART-RE was limited by lack of validation in other familial hypercholesterolemia populations.

SUBCLINICAL CORONARY ATHEROSCLEROSIS IN FAMILIAL HYPERCHOLESTEROLEMIA DURING THE STATIN ERA

Familial hypercholesterolemia individuals have an increased burden of subclinical coronary atherosclerosis (SCA) which is demonstrated by higher CAC prevalence, higher prevalence of coronary segments with atherosclerotic plaques and with luminal stenosis by CT in comparison with normolipidemic individuals [23–25,26²²]. The association between biomarkers and SCA is variable across different studies as those studies were mostly cross-sectional with relatively small sample sizes and variable familial hypercholesterolemia diagnosis based on clinical or molecular criteria. Moreover, a significant proportion of patients received previous statin therapy. Indeed, molecular diagnosis has implications for prognostic information and differences in subclinical atherosclerosis pattern. Clinical familial hypercholesterolemia diagnosis is based mainly on high LDL-C, personal history of early ASCVD and family history of high LDL-C and premature CHD, besides the detection of xanthomas and corneal arcus [1].

However, the presence of monogenic familial hypercholesterolemia-causing mutations is associated with a worse prognosis in comparison with other causes of severe hypercholesterolemia [20]. Sharifi *et al.* [21] extended this knowledge to subclinical vascular disease namely carotid intima media thickness (IMT) and CAC. The authors included patients with a clinical diagnosis of familial hypercholesterolemia and genotyped them in order to confirm monogenic or polygenic causes [21]. After adjustment for age and sex, the mean carotid IMT values and CAC scores were found to be higher in individuals familial hypercholesterolemia than in those with polygenic hypercholesterolemia carotid IMT mean: 0.74 vs. 0.66 mm , $P=0.038$ and CAC score mean: 24.5 vs. 2.65 Agatston units, $P=0.0004$ [21]. This may be explained by a greater time-weighted exposure to elevated LDL-C in familial hypercholesterolemia in comparison with polygenic hypercholesterolemia.

In SAFEHEART, 426 molecularly proven asymptomatic familial hypercholesterolemia individuals using statins for an average 11.9 ± 7.9 years (age 46 ± 10.5 years, treated LDL-C $176 \pm 63 \text{ mg/dl}$) underwent CT cardiac angiography [26²²]. The severity of SCA was evaluated with two parameters: stenosis defined as sum of stenosis severity (SSS) and plaque composition sum (PCS). Median 5-year and 10-year cardiovascular risk rates according to the SAFEHEART-RE were 0.6 and 1.3%, respectively. Fifty-six % of studied individuals presented with CAC and 22% had at least one luminal stenosis more than 50%. Of importance, only one individual in whom CAC

was absent presented luminal obstructions more than 50%. This study confirmed that CAC is associated with exposure to high LDL-C burden, that is a higher cholesterol year-score, as demonstrated previously [23,27]. SSS was independently associated with risk calculated by SAFEHEART-RE [β -coefficient: 1.6; confidence interval (95% CI): 1.1–2.1; $P < 0.001$]. The study also suggested an association between plaque composition and ASCVD risk factors. Importantly, detection of SCA led to treatment intensification as shown by a significantly higher use of combined statin and ezetimibe therapy, use of maximum doses of statins, higher reduction in LDL-C levels and more prevalent aspirin use in those patients [26^{***}]. During a mean follow-up of 2.7 years, there were 17 (4%) nonfatal events (two acute coronary syndromes and 15 ischemia-driven coronary revascularizations) and two (1%) fatal events. These events were associated with a greater burden of subclinical coronary disease as indicated by higher CAC scores, SSS and PCS. The study nevertheless was limited by the small number of events and short follow-up.

CORONARY ARTERY CALCIFICATION AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE EVENTS IN STATIN-TREATED FAMILIAL HYPERCHOLESTEROLEMIA INDIVIDUALS

Miname *et al.* [28^{***}] followed 206 molecularly proven asymptomatic familial hypercholesterolemia

individuals (mean age 45 ± 14 years, of whom two thirds were women, with baseline and on-treatment LDL-C 269 ± 70 and 150 ± 56 mg/dl, respectively) for a median of 3.7 years (interquartile range: 2.7–6.8 years). At baseline, 68.9% of patients had used statins for an average 7.7 ± 6.9 years, which increased to 96.6% at follow-up. Almost half of patients had CAC scores of 0 ($n = 101$), whereas 30% ($n = 62$) had CAC scores between 1 and 100 and 21% ($n = 43$) had CAC scores more than 100 Agatston units. During follow-up, 15 ASCVD events (7.2%) were documented, corresponding to 16.6 events/1000 person-years. Half of these were hard endpoints defined as death, myocardial infarction, ischemic stroke and unstable angina requiring revascularization. There was a graded association of higher CAC with a greater burden of ASCVD risk factors: older age, higher LDL-C, higher prevalence of hypertension, family history of premature CHD and presence of corneal arcus. Of importance, there were no differences in on-treatment LDL-C among groups. In univariate Cox regression analysis, male sex, family history of premature CHD, corneal arcus, lower HDL-C and CAC were all associated with ASCVD. However, in a multivariate model, only CAC remained independently associated with incident ASCVD events, with hazard ratio 3.33 (95% CI 1.635–6.790, $P = 0.001$). The annualized rate of ASCVD events per 1000 persons increased with higher CAC: for CAC scores grouped as 0, 1–100 and more than 100 Agatston units (Fig. 1) [28^{***}].

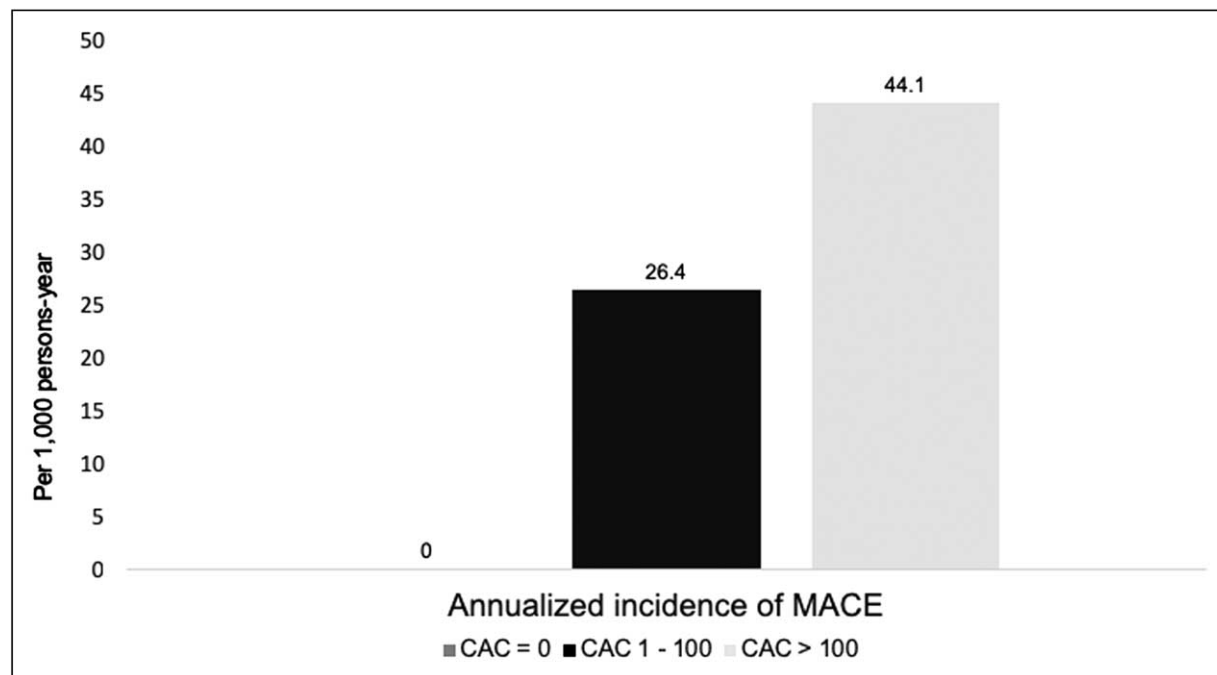


FIGURE 1. Annualized incidence of MACE in familial hypercholesterolemia according to CAC scores [28^{***}]. CAC, coronary artery calcification; MACEs, major atherosclerotic cardiovascular events.

CAC zero was associated with no events during follow-up ($P=0.003$).

The most important messages of this study were there was heterogeneity in subclinical atherosclerosis in familial hypercholesterolemia individuals, with roughly 50% of individuals presenting with no subclinical disease, numbers similar to those encountered by Perez de Isla *et al.* [26^{***}] (approximately 45%) in a larger population; a CAC score of zero was associated with no events occurrence during intermediate-term follow-up; and presence of CAC was the sole independent biomarker associated with clinical events. This study suggests that CAC may be useful in ASCVD risk stratification in heterozygous familial hypercholesterolemia patients treated with conventional lipid-lowering therapy in whom elevated residual LDL-C persists. Familial hypercholesterolemia individuals with greater CAC burden have higher ASCVD risk and possibly would derive greater benefit from more intensive lipid-lowering therapy with PCSK9 inhibitors. The contrary may also be true, at least in the intermediate term; CAC scores of zero meant no ASCVD events in statin-treated heterozygous familial hypercholesterolemia individuals. The corollary of this latter finding is that PCSK9 inhibitor treatment might be postponed or not even prescribed for these individuals. However, the results cannot be considered definitive because of the relatively small number of events and relatively short follow-up. One issue of interest is that CAC scores had apparent value in risk stratification even considering that LDL-C reduction induced by both statin therapy and PCSK9 inhibition with evolocumab is associated with increments in plaque calcification [29^{*}].

CONCLUSION

Heterozygous familial hypercholesterolemia is associated with an elevated risk of ASCVD. This excessive risk is greater in individuals aged 25–39 years with a trend to reduction over time because of statin treatment. The risk is heterogeneous and depends not only on high LDL-C, but also on other biomarkers. Clinical risk scores like the Montreal risk score and the SAFEHEART-RE seem promising in evaluating ASCVD risk in familial hypercholesterolemia individuals undergoing statin ± ezetimibe therapy but need further validation. Similar to clinical disease, coronary subclinical atherosclerosis, a marker of higher ASCVD risk in the general population, is also heterogeneous in familial hypercholesterolemia individuals. The study of Miname *et al.* [28^{***}] opens the possibility for further investigations of the role of CAC or computed tomography angiography in identifying primary prevention familial

hypercholesterolemia individuals undergoing conventional lipid-lowering therapy who could benefit or not from additional LDL-C lowering by PCSK9 inhibitors. If confirmed in more robust studies, the association between absence of CAC and reduced risk of ASCVD events might help in appropriate utilization and in improving cost-effectiveness of these treatments. Further studies are necessary to test the role of clinical scores as well detection of subclinical atherosclerosis in ASCVD risk evaluation in heterozygous familial hypercholesterolemia patients.

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Conflicts of interest

There are no conflicts of interest.

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