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Editorial

Difficulties in gauging atherosclerotic cardiovascular disease risk heterogeneity in familial hypercholesterolemia

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Familial hypercholesterolemia (FH), an autosomal co-dominant disease affecting overall 1:250–300 people, causes early atherosclerotic cardiovascular disease (ASCVD) and mortality [1]. Even recognizing that the risk attributable to FH is higher than the one of the general population [2], a fact seen even among those with severe hypercholesterolemia (i.e., LDL-cholesterol > 190 mg/dL) [3], the onset of ASCVD is heterogenous among people with the disease [1,4–7]. This is especially seen in contemporary heterozygous FH populations in use of statin therapy [2,7–9]. However, despite the latter, most affected FH people still have elevated LDL-cholesterol [10], and there is room for further cholesterol lowering with potent PCSK9 inhibitors [11]. Unfortunately, these drugs are not commonly reimbursed in many health systems. The use of risk stratification tools may therefore help increase the cost-effectiveness of novel lipid lowering therapies and thus increase access to those who most need them in cost-contained health environments [12].

Risk heterogeneity in heterozygous FH may be explained not only by higher cholesterol levels but also by the presence of previous ASCVD or other biomarkers like smoking, low HDL-cholesterol and high lipoprotein(a) [Lp(a)] concentrations, hypertension, diabetes, obesity and late onset of lipid lowering therapies among other factors [4] (Fig. 1). Despite being an elevated penetrance autosomal dominant disease determining high LDL-cholesterol from birth, other genes may also influence the course on ASCVD in FH as shown by Fahed et al. [5]. In the study the probability of ASCVD in those with FH monogenic defects varied from 17% to 79%, respectively, in those at lowest and highest percentiles of the non-LDL-cholesterol polygenic risk score. ASCVD risk is also higher in those presenting subclinical coronary atherosclerosis detected by coronary artery calcification (CAC) [7,9], a marker of atherosclerosis plaque burden, after median 2.7–3.7 years of follow-up in molecularly proven FH individuals, most of them using statin therapy.

Despite this, most physicians need to make decisions without availability of genetic and/or imaging tools, therefore, simple risk equations would be of extreme value to gauge ASCVD risk. Unfortunately, tools like SCORE or US pooled risk equations (PRE) widely used in the general population in Europe or in the USA were not meant for people with FH since they do not adequately consider the elevated cholesterol burden of the disease [1].

The SAFEHEART-risk equation (SRE) was developed in a contemporary Spanish cohort of 100% molecularly proven FH individuals, with more than 80% undergoing lipid lowering therapies (mean treatment duration 12.9 years) [6]. In the pioneer study of Perez de Isla et al. 2404 individuals with FH (45.2% males, mean age 45.5 years, mean baseline LDL-cholesterol 178 mg/dL) were followed by a mean of 5.5 ± 3.2 years and 0.5% (n = 12) and 5.1% (n = 122) suffered respectively from fatal and non-fatal events. Equations were derived for prediction of events in people presenting previous or not ASCVD manifestations and encompassed parameters like age, sex, previous ASCVD, blood pressure, body mass index, smoking, and LDL-cholesterol and Lp(a) concentrations. Equations to predict risk in 5 and 10 years presented a Harrel C index of 0.8 and had better discrimination for ASCVD than both Framingham risk scores (FRS) and PRE.

The SRE was tested in French FH individuals from the REFERCHOL registry (n = 1,463, 48.3% males, mean age 49.6 years, 70% with molecular diagnosis, baseline LDL-cholesterol 200 mg/dL). After a mean 3.9 ± 3.4 years of follow-up, 10.3% suffered from ASCVD events (n = 152). The derived SRE equation was further tested in 512 patients where 20.1% suffered from non-fatal ASCVD events and showed an area under the receiver operating characteristic (ROC) curves of 0.77 for 5-year event prediction. The authors also derived a simpler risk tool using the cholesterol-year score that had similar performances to the SRE. Finally, Paquette et al. developed the FH-Risk-Score and compared it to the SRE on a multinational population from North America and Europe (n = 3,881, 45% males, mean age 43 years, 74% with molecular

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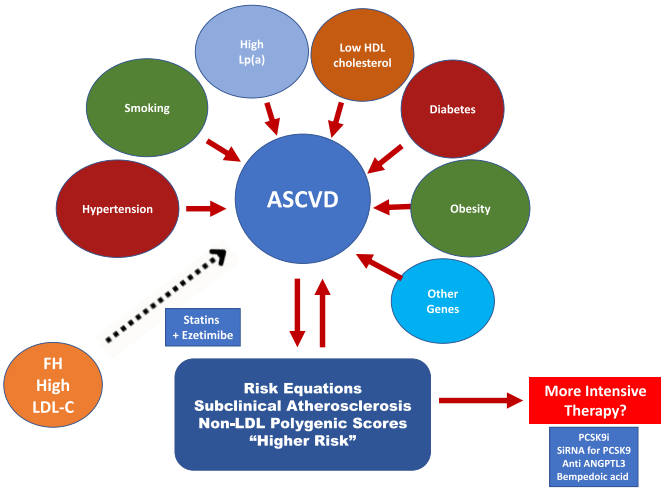

Fig. 1. Risk stratification in heterozygous familial hypercholesterolemia. ASCVD risk is heterogeneous and depends not only on LDL-cholesterol but also on other biomarkers and can be gauged by risk equations, coronary subclinical atherosclerosis and non-LDL-cholesterol polygenic risk scores. All patients with FH should receive statins and ezetimibe. In cost-contained environments, higher risk individuals would have preference for additional LDL-cholesterol lowering therapies to improve cost-effectiveness. PCSK9i-monoclonal PCSK9 inhibitors (evolocumab and alirocumab); siRNA small interfering RNA molecules (inclisiran); anti ANGPTL3-inhibitors of angiopoietin-like 3 protein (evinacumab).

diagnosis, baseline LDL-cholesterol 257 mg/dL). After a mean 8.0 ± 9.0 years of follow-up, 9.8% of study subjects had (n = 383) events. Of interest, all participants were in primary prevention and the Harrell C-index for 10-year ASCVD events was 0.75 and 0.69 for the FH-Risk-Score and the SRE, respectively. Additionally, in the tested population, the SRE calibration (i.e., predicted vs. actual risk) was considered suboptimal. Of importance, this study was the one with the longest follow-up and highest number of events tested so far [6,13–15].

In the current issue of *Atherosclerosis*, McKay et al. [15] evaluated the SRE performance in a historical cohort of patients followed in UK primary care clinics (n = 3,643, 57% males, mean age 51 years). In most FH was diagnosed by clinical criteria, mean available LDL-cholesterol was 141 mg/dL and 68.8% used lipid lowering therapies. After a median 3.73 years of follow-up, (interquartile ranges 1.59–6.48) years, 4.04% (n = 147) had vascular events corresponding to a 10-year event rate of 6.25% and 11.28%, respectively, for females and males. In this population, SRE presented a borderline discriminatory value with Harrell's C index of 0.67 (should be at least 0.70). Furthermore, the equation showed inadequate calibration between predicted and real occurrence of events (i.e., both 10 and 5-year risks were underpredicted). The authors recalibrated the equations for their population but, even so, SRE showed only a 10–30% net benefit in predicting risks. The authors concluded that despite recalibration SRE would have limited generalizability and moderate utility for the studied population.

The study is important since there is need to test the generalizability of proposed ASCVD risk tools in different FH populations and clinical practices. It main strengths reside on the fact that it was done in an environment representing FH clinical care in the UK, and by the robust statistical methods used.

Perez de Isla et al. [6]. were pioneers in proposing one simple robust risk equation to gauge ASCVD risk heterogeneity in FH, however, as it has been seen from this [15] and previous studies, one size seems not to fit all [13,14]. McKay et al. [15] recognize the differences between theirs' and the SAFEHEART population that may have affected study results e.g., 1-low availability of molecular diagnosis, meaning that forms of severe hypercholesterolemia but with a lower risk than FH may have been included in the cohort [3]; 2-lower LDL-cholesterol concentrations and differences in use of lipid lowering therapies facts that may affect ASCVD natural history [4]; and 3- absence of Lp(a) evaluation, an independent biomarker of ASCVD risk in FH [16,17]. One may add a relatively small number of ASCVD events and relatively short follow-up. However, the latter also occurred in the other cohorts [6,13] except the one from Paquette et al. [14]. Differences in studied population and impact of therapies may explain in part the study results. Indeed, the proven presence of molecular defects, not seen in 100% of people in the other cohorts [13,14], and long-term lipid lowering therapies may have made SAFEHEART a population where natural history is determined not only by the presence of a true genetic disease but also by the influence of almost 13 years of previous lipid lowering therapy on natural history of ASCVD [6].

Considering these heterogenous findings, how should one proceed with risk evaluation in people affected by FH? Should one rely or not on risk equations to stratify ASCVD risk? Previously, we had proposed that past ASCVD clinical manifestations, very high LDL-cholesterol concentrations, the presence of other risk biomarkers and subclinical coronary atherosclerosis would help identify higher risk people that could benefit from more intensive LDL-cholesterol lowering with PCSK9 inhibitors [4]. That may indeed be the case [18], however, a limitation of this proposal is that it does not necessarily define an absolute tangible value for the risk (i.e. X% ASCVD risk in X years), something that risk equations were meant to. To reduce the limitations of the latter, studies like the one from McKay et al. [15]. are important to show how proposed tools perform in different populations. Indeed, longer term follow ups, more ASCVD events, and multicentric studies are needed to improve accuracy of risk equations in FH.

Another way to improve accuracy of these equations may be by mixing them with detection of subclinical atherosclerosis [19]; indeed Gallo et al. demonstrated that CAC helps improve risk discrimination and reclassification on top of the SRE in the very same SAFEHEART and REFERCHOL populations [9]. CAC may work as a surrogate to cholesterol-year score and individual susceptibility to atherosclerosis development [1,12]. Previously, Miname et al. [20]. had suggested that a CAC score derived vascular age performed better than biological age in discriminating higher from lower risk of ASCVD in 206 molecularly proven FH individuals in Brazil. Vascular rather than biological age increased the ROC curve of the Framingham Risk Score (an equation no meant for people with FH) from 0.70 to 0.88 in predicting ASCVD events. One possible caveat of CAC scores is that statins, that are almost a ubiquitous therapy for people with FH, may increase plaque calcium density [21] and therefore, CAC progression may not necessarily mean disease progression, however, studies indicate that CAC maintains prognostic information even in those using statins [9,20,22].

FH is associated with high ASCVD risk; however, this risk is heterogenous, and stratification may help change natural history of this disease in a cost-effective manner (Fig. 1). Congratulations to McKay et al. [15]. for their study and more initiatives like that are needed.

Declaration of interests

MHM-none to declare; RDS has received honoraria related to consulting, research and/or speaker activities from: Abbott, Ache, Amgen, Amryt, Astra Zeneca, Biolab, Esperion, Eli-Lilly, Getz Pharma, Hypera Farma, Kowa, Libbs, Novo-Nordisk, Novartis, Merck, Pfizer, PTC Therapeutics and Sanofi.

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