Editorial

Simon Broome confirms that the IAS definition of severe familial hypercholesterolemia predicts coronary mortality in patients with FH

Familial hypercholesterolemia (FH) is a frequent genetic disorder that increases the risk of atherosclerotic cardiovascular disease (ASCVD) [1–4]. Statins reduce LDL-C in FH patients and observational data suggest that this prevents ASCVD and mortality [4–6]. However, residual risk persists, and this may partly relate to many FH patients not attaining recommended LDL-C goals. For example, in the contemporary Spanish Familial Hypercholesterolemia cohort study (SAFEHEART) [7] only 11% of patients reached an LDL-C < 2.5 mmol/L, in spite of the maximal standard cholesterol lowering therapy with statins ± ezetimibe. Therefore, novel and efficacious medications that further reduce LDL-C beyond conventional therapies have been approved for refractory patients [1,8]. Unfortunately, use of the latter, especially inhibitors of proprotein convertase subtilisin kexin type 9 (PCSK9), is restricted in most countries owing to the high cost of treatment and lack of reimbursement [8].

In spite of the widely accepted increased life-time risk of ASCVD in FH, it is less well recognized that risk is heterogeneous and dependent on several factors internal and external to the condition. ASCVD risk in FH depends not only on exposure to very high plasma LDL-C concentrations (> 8 mmol/L and especially > 10 mmol/L), but also on the presence of smoking, low HDL-C, hypertension, diabetes, prematurity of coronary artery disease (CAD) in first degree relatives, obesity and chronic kidney disease [3,8,9], as well as other genetic factors, including high lipoprotein(a)[Lp(a)] [10–13]. Finally, the presence of established or subclinical CAD also enhances the risk of ASCVD despite best standard of care [14,15]. Given the above evidence, two risk prediction equations have been proposed to increase the precision of risk stratification of FH individuals [11,16]. These equations, however, need further validation in diverse populations and appropriate recalibration to allow their wider use as precision medicine tools in the care of FH.

Considering the above, and the overlap of LDL-C concentrations between homozygous and heterozygous FH patients [17,18], a panel of experts was convened in 2016 by the International Atherosclerosis Society (IAS) to develop a position statement for defining an FH phenotype at higher risk of ASCVD, so called severe FH [8]. The panel recommended that, independent of genotype, FH patients at greater ASCVD risk with persistently elevated LDL-C concentrations above a treatment target should be considered as candidates for PCSK9 inhibitors and lipoprotein apheresis (Table 1). However, since the IAS definition was based on expert opinion and was not prospectively validated, criticisms were raised concerning its value in clinical practice [19]. In one cross sectional evaluation, Perez-Calahora et al. suggested that, in addition of being too broad since over half of men and women fulfilled the severe FH criteria, the IAS definition did not change risk stratification and indications for treatment, the exception being use of LDL-C > 10 mmol/L criterion irrespective of other risk factors.

In this issue of *Atherosclerosis*, Humphries et al. prospectively evaluated the association of severe FH, according to the IAS definition [8], with CAD mortality in heterozygous FH individuals followed between 1992 and 2016 in the UK's Simon Broome registry [20]. The authors studied 2929 definite (DFH) or possible (PFH) FH patients (51% women) aged 20–79 years recruited from 21 UK lipid clinics. Severe FH was defined using LDL-C levels and the presence of high-risk features as shown in Table 1; biomarkers such as Lp(a) and creatinine or coronary artery imaging were not considered, however. The investigators compared the excess CAD standardized mortality ratio (SMR) of severe and non-severe FH patients with that of the general England and Wales population. Approximately 70% of patients met the definition of severe FH. As previously shown, FH individuals as a whole had a higher SMR for CAD mortality compared with the general population [4]. However, CAD mortality was 64% higher ($p = 0.007$) in the severe phenotype of FH than in non-severe phenotype. The higher mortality risk was attributed to the greater burden of non-cholesterol risk factors in severe FH individuals.

The SMR for CAD at follow-up tended to be reduced in severe FH probably due to introduction of more effective lipid lowering therapy as previously suggested by the authors [4]. However, the SMR was still

Table 1

Severe familial hypercholesterolemia criteria and lipid lowering strategy according to 2016 IAS Panel [8].

At presentation (untreated LDL-C)	LDL-C and risk factors/features criteria	Treatment goal/strategy
	LDL-C > 10 mmol/L LDL-C > 7.5 mmol/L + 1 high risk feature LDL-C > 5 mmol/L + 2 high risk features	Realistic goal: reduce ≥50% LDL-C Ideal goal: LDL-C < 2.5 mmol/L If statins ± ezetimibe not enough, add PCSK9 inhibitors initially (If persist not at goal consider lomitapide approved for homozygous FH and lipoprotein apheresis)
Presence of advanced subclinical coronary atherosclerosis		
	Coronary artery calcium (CAC) score > 100 Agatston units, or > 75th percentile for age and sex[a] or computed tomography angiography (CTA) with obstructions > 50% or presence of non-obstructive plaques in more than one vessel	Realistic goal: reduce ≥50% LDL-C Ideal goal: LDL-C < 1.8 mmol/L If statins ± ezetimibe not enough, add PCSK9 inhibitors initially (If persist not at goal consider lomitapide approved for homozygous FH and lipoprotein apheresis)
Presence of clinical atherosclerotic cardiovascular disease	Defined as previous myocardial infarction, angina, coronary revascularization, non-embolic ischemic stroke, or transitory ischemic attack, and intermittent claudication	Realistic goal: reduce ≥50% LDL-C Ideal goal: LDL-C < 1.8 mmol/L If statins ± ezetimibe not enough, add PCSK9 inhibitors initially (If persist not at goal consider lomitapide approved for homozygous FH and lipoprotein apheresis)

High risk features: older age (Men: ≥30 years Women: ≥45) or > 40 years without treatment, male sex, smoking, low-HDL-cholesterol (< 1 mmol/L), hypertension, body mass index > 30 kg/m^2, diabetes mellitus, family history of early cardiovascular disease in first degree relatives (< 55 years old in males and < 60 years old in females), chronic kidney disease (defined as an estimated glomerular filtration rare < 60 ml/min/1.73 m^2 and Lp(a) > 75 nmol/L (50 mg/dL).

[a] Multiethnic study on atherosclerosis-MESA criteria (http://www.mesa-nhlbi.org/calcium/input.aspx).

higher in women with severe FH, suggesting that either cholesterol lowering therapy was not totally effective in controlling LDL-C or might have been started too late to adequately reduce CAD events. The treatment inequalities in coronary prevention that may disadvantage women with FH merit further investigation.

Another point of interest is that there was a higher frequency of severe FH individuals in those categorized as DFH rather than PFH according to the Simon Broome diagnostic criteria [20]. Among patients with definite FH, the IAS severe FH phenotype was associated with higher SMR for CAD than a non-severe phenotype 76%, in contrast to 26% in those with the severe phenotype in the PFH group. This was probably due to the inclusion of a greater number of "real" FH individuals with monogenic disease rather than lower risk individuals with polygenic hypercholesterolemia in the DFH group [10,21]. Indeed, one of the limitations of the study was that a molecular diagnosis of FH was not made in most individuals.

The main objective of risk stratification in FH is to identify higher risk individuals that could be more cost-effectively treated with novel therapies, especially PCSK9 inhibitors. As pointed out by the authors, the use of the IAS severe FH definition could reduce the number of patients requiring a PCSK9 monoclonal antibody to further LDL-C reduction, according to NICE recommendations, from 24% to 16%, the consequences of which need confirmation.

In spite of its value, the main limitation of the study by Humphries et al. is the low absolute mortality rates during follow-up, which might have related to effects of statin treatment. Hence, while it is encouraging to evidence the value of the IAS definition of severe FH using data from an established registry, further confirmation is required in other FH samples from international registries to generalize the results. Ultimately, the real value of the IAS definition can only be verified by unbiased data demonstrating that its implementation leads to better care and improves ASCVD and CAD outcomes in patients with FH.

Conflicts of interest

RDS has received honoraria related to consulting, speaker and/or research activities from:

Akcea, Amgen, Astra Zeneca, Biolab, Esperion, Kowa, Merck, Novo-Nordisk and Sanofi/Regeneron.

GFW has received honoraria related to consulting, speaker and/or

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