

## **Defining severe familial hypercholesterolemia: Implications for clinical management**

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## **Summary**

Familial hypercholesterolemia (FH) is highly represented in cohorts of individuals who suffered from a myocardial infarction at young age. Recent data suggest that the prevalence of heterozygous FH may be as high as ~1:200 and that of homozygous FH as high as~ 1:300,000. There is considerable overlap between the phenotypes of heterozygous and homozygous FH and the response to treatment is also heterogeneous. Here, we aim to define a severe FH phenotype, based on a very high plasma LDL-cholesterol level and responsiveness to conventional lipid lowering treatment. We evaluate the importance of molecular characterization and define the role of other cardiovascular risk factors and advanced coronary subclinical atherosclerosis in risk stratification. Individuals with severe FH may particularly benefit from early and more aggressive cholesterol lowering therapy with recently approved medications especially PCSK9 inhibitors. In addition to better tailored therapy, more precise characterization of severe FH individuals could improve resource utilization.

## **Introduction: challenging classical concepts in familial hypercholesterolemia**

Familial hypercholesterolemia (FH) is an autosomal co-dominant disorder characterized by elevated blood low-density-lipoprotein cholesterol (LDL-C) concentrations and an average three to thirteen-fold greater risk of premature atherosclerotic cardiovascular disease (ASCVD) compared to normolipidemic individuals<sup>1-3</sup>. FH has been subclassified into heterozygous (He) and homozygous (Ho) forms depending on the presence of one or two affected alleles in genes encoding the LDL receptor (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin kexin type 9 (PCSK9)<sup>1,3</sup>. Clinical diagnosis is made on the basis of elevated LDL-C levels: HeFH and HoFH patients usually present with LDL-C levels two- to three-fold and up to ten-fold higher than normal, respectively<sup>3,4</sup>. With the exception of regions where founder effects are present (e.g. South Africa, Quebec, Lebanon among others), new evidence suggests that HeFH affects 1 in ~ 200-600 individuals<sup>2,5,6</sup>. HoFH, initially described to affect 1:1,000,000<sup>7</sup>, is probably three times more prevalent than previously thought<sup>4,8</sup>.

Patients with the HoFH phenotype are considered at the highest level of risk for ASCVD<sup>7,9</sup>. However, with more widespread use of molecular diagnosis it is now evident that some subjects carrying heterozygous mutations in FH genes have LDL-C values that overlap those considered to be characteristic of HoFH (usually > 10-13 mmol/L or 400-500 mg/dL)<sup>1,4</sup> and therefore should also be considered at very high risk<sup>8,10-12</sup>. The converse also applies, with

molecularly proven HoFH patients presenting with LDL-C in the range typical of heterozygotes<sup>8,12-14</sup>. The complex reasons for phenotypic heterogeneity among individuals with the same FH genotype have recently become apparent. LDL-C levels are influenced not only by rare, large-effect monogenic variants but also by common small-effect gene variants; this notion adds complexity to the currently used diagnostic classification<sup>15,16</sup>. Since LDL-C levels, and not the causative FH mutations or spectrum of variants are the main drivers of ASCVD risk<sup>17</sup>, a definition of the severe FH phenotype encompassing those at high risk needs to be considered for best clinical practice<sup>11</sup>. This definition should not be defined by whether or not HeFH or HoFH is diagnosed based on a molecular test. FH patients with previous ASCVD manifestations, those with advanced subclinical atherosclerosis, and patients with LDL-C > 8 mmol/L (310 mg/dL)<sup>18</sup> associated or not with other risk conditions at initial presentation are at particularly high-risk.

The currently available effective standard lipid lowering therapies (high dose statins, and ezetimibe mainly)<sup>1,4</sup>, together with emergence of newer, efficacious but more expensive treatments like mipomersen<sup>13,19</sup>, lomitapide<sup>14</sup> and PCSK9 inhibitors emphasizes the need for case identification<sup>20</sup>. Indeed considering cost-effectiveness<sup>21,22</sup> PCSK9 inhibitors may have particular benefits in FH subjects considered being at the highest level of ASCVD risk with persistent and recalcitrant elevated LDL-C concentrations despite treatments. These medications should be started early after refractoriness to conventional treatment is shown (realistically a LDL-C reduction < 50%) and

be used indefinitely if tolerated in order to attain proposed LDL-C goals (e.g. ideally < 2.5 or 1.8 mmol/L or 100 and 70 mg/dL) according to presence or absence of ASCVD.

This paper arose from the need to address the gap created by the knowledge that ASCVD risk in FH is directly related to chronic exposure to elevated LDL-C and newer information regarding genetic diagnosis of severe FH, where the prior stratification of unaffected, heterozygous, or homozygous for FH no longer adequately describes risk because of overlap in LDL-C levels across these categorizations. With the availability of new medications to effectively lower LDL-C and the absence of an evidence base that directly addresses the issue of genetic heterogeneity, the International Atherosclerosis Society (IAS) convened an expert panel to establish consensus regarding clinical recommendations for this high-risk population. In this review, we address ASCVD risk stratification and treatment recommendations for these patients, including timing, intensification, goals, and choice of therapy.

## **Methods**

### *Search strategy and selection criteria*

This document is based on a search of primarily English language literature since January 1980 on the terms FH, hypercholesterolemia, subclinical atherosclerosis and cholesterol lowering treatment from PubMed together with the consensus of opinion from an international panel of dyslipidemia specialists that was convened by the IAS, which worked together from March 2015 to March 2016. We emphasize that there are limited prospective data in FH populations and that most of the cited studies are observational cross-

sectional or historical cohorts of patients. Also, due to lack of specific studies some of the recommendations made by the panel come from consensus opinions derived from studies performed in the general population. The panel met in Amsterdam the Netherlands, to present and discuss available data in May 2015 and worked thereafter electronically to finalize this expert opinion consensus.

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### **Importance of sustained high LDL-cholesterol as a risk factor for atherosclerotic cardiovascular disease and its deleterious role in familial hypercholesterolemia**

Elevated blood cholesterol is an independent cause of ASCVD. This evidence comes from prospective observational studies<sup>23</sup>, from genome wide association studies (GWAS)<sup>24</sup> and from mendelian randomization studies<sup>25,26</sup>. The definitive proof of the causal role for cholesterol in ASCVD derives from numerous robust clinical and surrogate interventional studies with cholesterol lowering medications, mainly statins,<sup>27,28</sup> that showed reduction in major atherosclerotic cardiovascular events (MACE) and mortality.

Owing to the extremely high plasma LDL-C levels, HoFH patients are considered to be at the highest level of risk for early ASCVD, which may be

up to 100 times higher than the risk in the general population <sup>7,9</sup>. HoFH individuals frequently develop aortic or supra-aortic valve stenosis in addition to atherosclerosis in the aorta, coronary, carotid and peripheral arteries <sup>7</sup>.

The concept of the cholesterol-year score, a marker of exposure to high cholesterol levels over time underpins the pathogenic relationship between chronically elevated LDL-C and extensive atherosclerosis in young FH patients <sup>5,29-31</sup>. High plasma LDL-C is associated with a worse prognosis in both HoFH and HeFH <sup>18,31,32</sup>. If untreated, FH is particularly devastating among younger individuals, as shown in the pre statin era, where 125 and 48-fold increases in adjusted mortality rates were described in women and men respectively, in the 20- to 29-year-old age stratum compared with normolipidemic individuals <sup>33</sup>. Recently, Do and co-workers sequenced the protein-coding regions of 9,793 genomes from patients with early myocardial infarction and found that 2% of cases were caused by LDL receptor damaging mutations <sup>34</sup>. Similarly, Nanchen et al. <sup>35</sup> found that 4.8% of 1,451 individuals aged < 60 years presenting with an acute coronary syndrome had either probable or definite FH.

Even among more recent reports that include treatment with statins, individuals with the HoFH phenotype disappointingly still live with an extremely high risk of early ASCVD onset and premature mortality <sup>36,37</sup>. Raal et al. <sup>36</sup> evaluated the occurrence of MACE in 149 South African HoFH patients. They found that MACE occurrence was reduced by 51% after 1990, which was the year statins were introduced in that country. But even so, the

age of onset for the first MACE was postponed on average from 12.8 years to only 28.3 years, and by age 40 years almost 90% of studied patients had suffered a vascular event.

Thompson et al. recently reported long-term outcomes on 43 HoFH patients who had been treated at the Hammersmith Hospital in London, UK over the past 50 years<sup>37</sup>. The authors compared those who either did or did not die during the follow-up period. The use of statins and apheresis was more frequent in the survivors, and there was a clear temporal improvement in the care of HoFH patients over this period. However, despite this, ASCVD prevalence was still high in living HoFH patients: aortic stenosis was seen in 33%, aortic valve replacement required in 14% and, coronary heart disease was present in 37%. In both studies, on-treatment total cholesterol levels remained very high: average 13.1 and 8.1 mmol/L (505 and 320 mg/dL) respectively in the South African<sup>36</sup> and UK populations<sup>37</sup> confirming the importance of high cholesterol as the driver of ASCVD in HoFH and the huge unmet treatment need for this population.

Many HeFH individuals are at high ASCVD risk as well due to extremely elevated LDL-C that is relatively refractory to current lipid lowering treatments. LDL-C values > 8 mmol/L (310 mg/dL) prior to therapy have been suggested to identify a more severe HeFH phenotype<sup>18</sup> independent of the presence of traditional risk factors such as smoking, diabetes, hypertension or family history of early ASCVD. However, this risk was greater if associated with the other risk conditions. In a Dutch cohort, such elevated LDL-C values were

encountered in 1:3,000 or 11% of the Dutch FH population and were associated with a 1.36 odds ratio (95% CI: 1.09 to 1.69) for ASCVD compared to other FH patients. An LDL-C concentration > 8 mmol/L (310 mg/dL) that is refractory to maximally tolerated pharmaceutical therapy has also been suggested to be an indication for reimbursement of apheresis (either plasmapheresis or selective lipoprotein apheresis) in subjects without previous manifestations of ASCVD<sup>38</sup>.

#### *Late treatment onset and refractoriness*

Another important issue when assessing the severity of the FH phenotype is the age at initiation of treatment, later treatment, for instance after 40 years of age<sup>3,5,30</sup>, implies a longer exposure of the arterial wall to high LDL-C and consequently a greater risk of ASCVD.

Most guidelines endorse a minimum LDL-C reduction of 50% for FH patients, and often recommend specific absolute targets, such as LDL-C values < 2.5 (100 mg/dL) or 1.8 mmol/L (70 mg/dL) in individuals presenting with clinical ASCVD<sup>1,3,5</sup>.

In an earlier cross sectional evaluation of 1,249 well-treated and monitored HeFH patients from the Netherlands, Pijlman et al.<sup>39</sup> found that only 21% attained LDL-C levels < 2.5 mmol/L (100 mg/dL). More recently in the SAFEHEART Spanish FH cohort, Perez de Isla et al.<sup>40</sup> found in 2,170 molecularly defined HeFH patients, followed for an average of 5 years, that an LDL-C target <2.5 mmol/L (100 mg/dL) was reached in only 11.2% of

patients. In that study, 72% of FH cases were on maximum lipid lowering therapy defined as statin dose alone or combined with ezetimibe aiming to reduce LDL-C by at least 50%. Of those presenting previous ASCVD only 4.7% attained an LDL-C < 1.8 mmol/L (70 mg/dL). These results show the immense gap in controlling lipids in FH patients, particularly for secondary prevention of ASCVD.

### **Genotype, LDL-cholesterol levels and risk discordance**

An elevated LDL-C level is the *sine qua non* for the diagnosis of FH (e.g. > 5 mmol/L or 190 mg/dL for adults for HeFH), with increasing diagnostic confidence imparted by family history of hypercholesterolemia, personal or family history of premature ASCVD, and physical features, such as tendon xanthomas, arcus cornealis and xanthelasmas.<sup>1,5,41</sup>

Identification of a causative gene variant is not essential for either diagnosis or treatment decisions, since as mentioned these are more appropriately guided by the LDL-C and not by the genotype. More widespread use of genetic analysis to identify patients with FH has led to the discovery of a higher prevalence than expected of less severe forms of FH;<sup>4,5,8</sup> with lower LDL-C levels and less apparent physical findings. Several factors confound the genotype-phenotype relationship in FH and make the simplistic distinction between HoFH and HeFH not adequate for risk management: 1) heterogeneity of monogenic etiologies; 2) heterogeneous variant classes; 3) polygenic effects; 4) gene-gene interactions; 5) gene-environment

interactions; 6) modulatory roles for other unknown mendelian genes; and 7) non-mendelian genetic mechanisms including epigenetic effects.

### *Locus and mutation type heterogeneity*

It is well known that FH is typically inherited as a co-dominant autosomal disease caused by mutations within, in decreasing order of prevalence, the *LDLR*, *APOB* and *PCSK9* genes encoding the LDL receptor, apo B and PCSK9, respectively. <sup>5,41</sup> Next-generation sequencing has shown that the HeFH phenotype very occasionally results from dominant mutations in *APOE* or *STAP1* encoding apolipoprotein E, and signal transducing adapting family member 1, respectively. <sup>4,5</sup> The *LDLR*, *APOB* and *PCSK9* co-dominant genes also underlie the HoFH phenotype when two mutations are inherited. <sup>4</sup> Additionally, rare variants in *LDLRAP1* encoding the LDLR adaptor protein 1 cause a purely autosomal recessive hypercholesterolemia (ARH), in which heterozygous parents are phenotypically normal. Recessive forms of hypercholesterolemia phenotypically similar to HoFH have been reported with certain rare mutations in *LIPA*, encoding lysosomal acid lipase, and *ABCG5/G8*, encoding sterolin-1 and sterolin-2. Homozygosity or compound heterozygosity for such mutations classically cause cholesterol ester storage disease (or Wolman disease) and sitosterolemia (or phytosterolemia), respectively.

It is also known that, for *LDLR* variants, clinical phenotype severity depends on residual LDL receptor activity. <sup>5,41</sup> *LDLR*-negative or -null mutations are associated with <2% activity of the receptors and *LDLR*-defective mutations are associated with 2-25% activity.

Genetic heterogeneity in HoFH underlies phenotypic variability: LDLR-null HoFH patients have higher LDL-C levels and poorer clinical prognosis than LDLR-defective HoFH patients.<sup>31,42</sup> Across the spectrum of "severe hypercholesterolemia", mean LDL-C follows a decreasing gradient according to genotype: homozygous LDLR-null > compound heterozygous LDLR-null + LDLR-defective > homozygous LDLR-defective or LDLRAP1 > homozygous defective APOB or PCSK9 gain-of-function > double heterozygote (e.g. LDLR + PCSK9 gain-of-function or defective APOB) > HeFH (LDLR-null) > HeFH (LDLR-defective).<sup>4</sup>

Recent population-based molecular studies showed that only ~ 50% of carriers of two FH causative variants had LDL-C levels consistent with prior clinical diagnostic criteria for HoFH, i.e. >13 mmol/L (500 mg/dL)<sup>4, 8</sup>.

Remarkably, in many untreated carriers of two putative deleterious mutations, LDL-C levels were comparable to those generally observed in HeFH patients.

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The need for aggressive treatment - e.g. LDL apheresis, lomitapide, mipomersen or PCSK9 inhibition - in such cases depends on the LDL-C level, and not the molecular diagnosis. For instance, a carrier of two genetic variants who has plasma LDL-C in the HeFH range could be treated as a heterozygote, even though molecularly s/he has HoFH. Conversely some patients with only one heterozygous mutation detected may present with LDL-C levels consistent with the HoFH phenotype. Such genotype-phenotype discrepancies may be due to other factors beside the major locus effect

*Small-effect variants in hypercholesterolemia*

Causative variants are not found by DNA sequencing in 20-40% of patients with a probable or definite clinical diagnosis of HeFH according to clinical criteria.<sup>15</sup> Some of the missing variability is now attributable to polygenic effects, quantifiable by polygenic risk scores for high LDL-C.<sup>15</sup> These scores are determined by tallying the patient's burden of common LDL-C raising alleles from single nucleotide polymorphisms (SNPs) identified in GWASs of normolipidemic populations.

Some common small-effect loci are identical to large-effect monogenic FH loci, such as *LDLR*, *APOB*, *PCSK9* and *ABCG5/8*. Other small-effect loci, such as *HMGCR* encoding HMG-CoA reductase, make sense from a mechanistic perspective. Still others specify interesting new mechanisms, such as *SORT1* encoding sortilin 1<sup>15</sup>. Polygenic scores can be weighted according to effect sizes.<sup>15,16</sup> For instance, LDL-C is increased by ~0.25 mmol/L (~10 mg/dL) by common *LDLR* and *APOE* SNP alleles, but only by ~0.07 mmol/L (~3 mg/dL) by *PCSK9* SNP alleles. A high polygenic genetic risk score explains some, but not all, of "HeFH" patients who lack a monogenic large-effect mutation. A high polygenic risk burden also likely worsens the phenotype in large-effect FH mutation carriers. Interestingly, > 95% of children and adolescents diagnosed clinically with FH carry a large-effect mutation in a canonical FH gene; polygenic effects are not demonstrable in this age group.<sup>43</sup>

#### *Gene-gene and gene-environment interactions and epigenetic effects*

The severity of the phenotype among carriers of the same variant can be modulated by variation at other loci. For instance, the combined effect of

single *LDLR* and *APOB* mutations produces a phenotype intermediate between HeFH and HoFH.<sup>44</sup> Also, *APOE* genotype can modulate phenotypic expression in carriers of the same HeFH mutation.<sup>45</sup> In contrast, inheriting an *APOB* hypobetalipoproteinemia mutation normalized the lipid profile in a subject with causative HeFH mutation in *LDLR*.<sup>46</sup> In addition, the trend towards higher LDL-C levels among index cases of FH compared to more distant relatives suggests interaction with background polygenic or environmental effects.<sup>47</sup>

Other examples of gene-environment interactions include variable risk of death among HeFH patients in multigenerational families.<sup>48,49</sup> Such variability points to interactions with environmental factors; generational changes in activity level and dietary composition were considered to be the key modulatory influences.<sup>48,49</sup> Finally, a HeFH patient had very low LDL-C levels due to chronic hepatitis C virus infection, providing a different mechanism for external modulation of the FH phenotype<sup>50</sup>. Other possible sources of phenotypic variability in FH include epigenetic modifications, such as DNA methylation, which may be associated with perturbations of key lipoprotein metabolism genes and variable plasma lipid levels in carriers of identical HeFH mutations.<sup>51</sup>

### *Genotype-drug interactions*

LDL-C response to statin treatment is highly variable according to genotype status in FH.<sup>52</sup> For instance, attainment of target LDL-C levels was greatest in HeFH patients with no mutation (presumed polygenic), intermediate in patients with *LDLR*-defective mutations and worst in patients with *LDLR*-null

mutations, although the latter had the highest baseline LDL-C levels.<sup>53</sup> Other genetic determinants of response to statins have been reported.<sup>54</sup>

Genetic factors also modulate the response to PCSK9 inhibitors. Studies in HeFH patients who received alirocumab or evolocumab subcutaneously showed similar relative LDL-C reductions from baseline as in non-FH patients.<sup>20</sup> HeFH patients with LDLR-null mutations responded equally well to evolocumab (~55% reductions in LDL-C) as those with either LDLR-defective mutations or APOB mutations<sup>10</sup>, suggesting that response depends mainly on upregulation of the normal LDLR allele, with the mutant receptor contributing negligibly. In contrast, in HoFH PCSK9 inhibitors had no effect on LDL-C in individuals with two LDLR-null alleles, but if at least one allele had residual LDLR activity, PCSK9 inhibitors lowered LDL cholesterol by ~ 35%.<sup>55</sup> Thus, the genotype may predict response to PCSK9 inhibition in HoFH patients.<sup>10,55</sup>

### **Cardiovascular risk heterogeneity and stratification: defining the severe FH phenotype**

FH patients with a history of an ASCVD event are at the highest risk for event recurrence and mortality. This was clearly shown by Neil et al.<sup>56</sup> in 3,382 HeFH patients from UK clinics followed for 26 years. Notwithstanding an overall reduction in coronary heart disease mortality by 37% with statin therapy, the excess standardized mortality ratio in secondary prevention patients was still four-fold higher compared to the general population. The benefit was half that encountered in treated FH patients in the context of primary prevention. This emphasizes the need for early diagnosis and

intervention in FH, which is achievable with efficient cascade screening programs.

Despite the elevated lifetime ASCVD risk in FH, the risk is heterogeneous in primary prevention<sup>9,18,33</sup>. This is true even among individuals with the same FH-causing mutation<sup>57</sup>. In addition to higher LDL-C levels and late onset or refractoriness to treatment, conventional risk factors explain in part this ASCVD risk heterogeneity<sup>18,58-60</sup>.

#### *Presence of risk conditions for atherosclerosis other than elevated LDL-C*

Atherosclerosis is a multifactorial disease and risk conditions like onset of lipid lowering treatment > 40 years of age, male sex, smoking, low HDL-cholesterol (<1 mmol/L or 40 mg/dL), diabetes mellitus, hypertension, family history of early ASCVD in first degree relatives (< 55 years males and < 60 years in females), body mass index > 30 kg/m<sup>2</sup>, and chronic kidney disease (defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m<sup>2</sup>) are independently associated ASCVD risk in HeFH<sup>18,58-61</sup>.

Elevated plasma lipoprotein(a) [Lp(a)] concentrations seem to be particularly deleterious for FH patients<sup>58-60,62</sup>. High Lp(a) has been independently associated with coronary heart disease, ischemic stroke and aortic stenosis in meta-analysis of prospective studies<sup>63</sup>, GWAS<sup>64</sup> and in mendelian<sup>65</sup> randomization studies in the general population. Lp(a) is pro-atherogenic not only because it is a cholesterol-rich particle but also due to its pro-thrombotic and pro-inflammatory properties<sup>66,67</sup>.

Lp(a) levels are elevated in FH in comparison with normolipidemic subjects<sup>58,62,67</sup>, and very high levels are seen usually in HoFH<sup>67,68</sup>. This finding is remarkable in the light of the lack of definitive evidence of a crucial role of the LDL receptor in Lp(a) plasma clearance<sup>67,69</sup>.

Previous evidence associating Lp(a) with elevated ASCVD risk in FH<sup>59,60,62</sup> has been subsequently supported by observations from the SAFEHEART cohort<sup>58</sup> where Lp(a) levels > 50 mg/dL (75 nmol/L) were found associated the onset of ASCVD. Moreover, in asymptomatic, statin-treated FH patients, high Lp(a) level was an independent risk of aortic valve calcification, pointing at potential additional cardiac disease outside the coronary problems in long-term treated patients<sup>70</sup>.

#### *Advanced subclinical coronary atherosclerosis burden*

An advanced burden of subclinical atherosclerosis in the coronary arteries is an independent marker of ASCVD risk in the general population<sup>71-73</sup>. There is evidence from robust prospective studies that advanced coronary artery calcification detected by cardiac computed tomography, defined mainly as a coronary calcium score >100 Agatston units, identifies individuals at high relative and absolute risk of coronary heart disease events and mortality<sup>72,74</sup>. Coronary calcium scores > the 75<sup>th</sup> percentile for age and gender can also be used to identify individuals with an elevated atherosclerotic plaque burden and increased higher ASCVD risk<sup>75</sup>.

The presence of obstructive (>50% luminal obstruction) in one vessel or non-obstructive coronary plaques in at least two vessels detected by cardiac computed tomography angiography also represent independent markers of death and myocardial infarction<sup>73,76-78</sup>.

Indeed advanced subclinical atherosclerosis can be detected in FH patients cardiac computed tomography<sup>79-82</sup>. Recently, Tada et al.<sup>83</sup> evaluated prospectively 101 molecularly defined HeFH individuals, of whom 65-70% took statins for 7 to 9 years. After a median 941 days of follow-up, 21 major atherosclerotic events had occurred and an elevated coronary atherosclerotic plaque score (hazard ratio 3.65; 95% CI 1.32 to 25.84) was independently associated with coronary events.

Firm recommendations for the detection of advanced subclinical coronary atherosclerosis do not exist for either the general population or those with FH. At one extreme, those with homozygous FH and LDL-c > 10 mmol/L (400 mg/dL)<sup>1,4</sup>, often detected in childhood, require frequent monitoring for atherosclerosis. In less severe settings non-mandatory it could help identify higher risk FH individuals<sup>71</sup> for whom more intense lipid lowering treatment (LDL-C <1.8 mmol/L or < 70 mg/dL depending on treatment availability and toxicity) would be appropriate. Examples include those recognized in adulthood and thus untreated for many years and those with multiple ASCVD risk factors. Absence of subclinical disease should not preclude initiation of lipid-lowering treatment.

### *Risk stratification*

Table 1 depicts the proposed definition and lipid goals for patients with severe FH. Those with prevalent ASCVD have the highest risk. Detection of advanced subclinical atherosclerosis, depending on availability of such testing, indicates the need for more intensive LDL-C lowering therapy. Advanced subclinical atherosclerosis is defined as an elevated burden of subclinical atherosclerosis detected in the coronary arteries as shown in Table 1. In the absence of ASCVD or subclinical atherosclerosis, LDL-C is the greatest driver of ASCVD onset. Risk factors are additive thus the risk needs to be stratified according to LDL-C thresholds and a concomitant risk condition algorithm. Three LDL-C values were chosen to identify a severe FH patient: LDL-C >10 mmol/L (400 mg/dL), LDL-C > 8.0 mmol/L (310 mg/dL) + one high-risk condition and LDL-C > 5 mmol/L (190 mg/dL) + two high-risk conditions. These criteria were chosen based on the previously discussed clinical epidemiology and also considering the possible additive costs of newer treatments.

### **Treatments for severe familial hypercholesterolemia**

Table and figure 1 show respectively the panel's proposed LDL-C goals and treatment algorithm for severe FH. Table 2 resumes effectiveness, indications, treatment posology and side effects of lipoprotein apheresis and the recently approved pharmacological treatments for severe FH forms (e.g. PCSK9 inhibitors, lomitapide and mipomersen). Since in most situations severe FH patients have extremely elevated LDL-C levels, goals should be considered as realistic or ideal, depending on baseline LDL-C, treatment

availability, toxicity and costs. A realistic goal for these patients would be to achieve minimally a 50% reduction in LDL-C as previously proposed<sup>1,4,5</sup>. Generally, LDL-C reduction to < 2.5 mmol/L (100 mg/dL) would be the ideal target in adults. However, in the presence of previous ASCVD event or advanced subclinical atherosclerosis, a lower ideal treatment goal, <1.8 mmol/L (70 mg/dL), is proposed [add here references 4 and 5] based on epidemiology and data from clinical trials that included FH patients, but were not specific for this population<sup>27,84</sup>.

Considering the available evidence<sup>27</sup> LDL-C reduction must be attained initially with the highest tolerated statin dose with addition of ezetimibe<sup>28</sup>. Other drugs like bile acid sequestrants and niacin are optional, depending on availability and tolerability with the aim of reducing cholesterol in refractory patients who are not at goal.

### *PCSK9 inhibitors*

If patients are considered refractory (LDL-C reduction <50% and out of ideal goals) with conventional therapy, the panel acknowledges that PCSK9 inhibitors may be prescribed for reasons of efficacy, tolerability, and lower costs in comparison with mipomersen and lomitapide (these two last medications approved only for HoFH), and lipoprotein apheresis to treat severe FH. PCSK9 inhibitors should be started as soon as refractoriness to conventional treatment is detected, and should be maintained indefinitely, if well tolerated until proven otherwise. PCSK9 inhibitors have a great potential in controlling LDL-C levels in severe FH patients since LDL-C values < 1.8

mmol/L (70 mg/dL) were attained in 61-66% in refractory to standard lipid lowering therapy HeFH patients treated with evolocumab<sup>10</sup> and 60-68% in those receiving alirocumab<sup>20</sup>. In both alirocumab and evolocumab studies the drugs were well tolerated and side effects were not different from placebo. The potential of PCSK9 inhibitors in ASCVD prevention and their long-term safety is being tested in studies enrolling high-risk patients with a background of statin therapy like FOURIER (NCT01764633), ODYSSEY Outcomes (NCT01663402), SPIRE-1 (NCT01975389) and SPIRE-2 (NCT01975376)<sup>85</sup>.

#### *Mipomersen and lomitapide*

Both mipomersen, an antisense oligonucleotide that reduces the production of apolipoprotein B, and lomitapide a microsomal transfer protein (MTP) inhibitor, are approved (the former in the USA and the latter in both North America and Europe) for treatment of HoFH patients. These drugs can low LDL-C by 25-50% in HoFH patients<sup>13,14</sup>. They may be used in HOFH patients refractory to statin + ezetimibe and PCKS9 treatment e.g. those homozygotes due to null LDLR mutations<sup>55</sup>. It is important to emphasize that the use of mipomersen and lomitapide is restricted by their side effects and extremely elevated costs. Studies are necessary to evaluate the association of mipomersen or lomitapide with PCSK9 inhibitors.

#### *Lipoprotein apheresis*

Apheresis, either non-selective plasmapheresis or preferably selective LDL apheresis or lipopheresis is approved and reimbursed in some countries to lower LDL-C levels in high-risk individuals with refractory dyslipidemia<sup>86</sup>. Previous studies have associated the use of lipopheresis with reduction in

progression or regression of anatomical coronary disease<sup>38,86,87</sup>. A ten-year non-randomized study performed in Japan<sup>88</sup> in 130 HeFH patients suggests that apheresis decreases events when added to lipid lowering drugs.

Lipopheresis is indicated when pharmacological treatment is not efficacious in controlling severe FH patients.

#### *Future developments for the treatment of severe FH forms*

Orthotopic liver transplantation is associated with the dramatic correction and even resolution of the HoFH phenotype<sup>4</sup>. The disadvantages and risks of transplantation and long-term immunosuppression have limited the viability of this approach in this disease, but have given the rationale for the development of novel therapeutic approaches, such as liver-directed gene delivery or stem cell transplantation.

After decades of pre-clinical research<sup>89</sup>, a gene therapy trial utilizing an AAV-based vector carrying an LDLR transgene has been announced (NCT02651675). Autologous transplantation of genetically corrected cells derived from human induced pluripotent stem cells is also being tested, albeit this approach is still in preclinical stage<sup>90</sup>.

#### **Cost effectiveness issues**

The use of statins to prevent cardiovascular events in FH has been proven to be cost-effective. However, treatments for more severe FH cases can be extremely costly. The yearly cost of weekly intensive lipopheresis has been estimated at \$100,000<sup>91</sup>. Mipomersen and lomitapide cost respectively

\$176,000 and between 235,000–\$295,000 per year<sup>22</sup>, while PCSK9 monoclonal antibodies cost ~ \$14,000 per year in the USA (but about half this cost in Europe and Canada)<sup>21</sup>. The use of these expensive treatments certainly can impose an elevated burden to health systems especially for developing countries where FH is severely underdiagnosed<sup>5</sup>. Therefore the characterization of higher-risk individuals, the maximization of standard treatment use and the judicious use of those treatments following a step-by-step protocol as shown in Figure 1 could attenuate these costs as long as intensive LDL-C reduction effectively reduces the risk of these events.

## **Conclusions**

Essentially everyone with FH lives with increased life-time risk for ASCVD. Among those with FH, a group with enhanced risk can be identified. In addition to patients with symptomatic ASCVD, they include those with the highest levels of LDL-C (irrespective of a molecular HeFH or HoFH diagnosis), those with advanced subclinical atherosclerosis, and those with additional ASCVD risk factors. For these severe FH patients treatment should be initiated with statins plus ezetimibe, and other conventional treatments as tolerated. If treatment goals are not met then newer agents including PCSK9 inhibitors, lomitapide, and mipomersen, should be considered. Other risk factors for ASCVD like smoking, or a sedentary life style must also be aggressively treated in this high-risk population. Those FH individuals with existing ASCVD should be treated aggressively and to achieve LDL-C targets earlier institution of treatment with newer agents is likely necessary.

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**Table 1: Proposed Criteria for Definition of Severe Familial Hypercholesterolemia**

**With Confirmed Heterozygous or Homozygous Familial Hypercholesterolemia**

<b>Presence of clinical atherosclerotic cardiovascular disease</b>		Realistic goal: reduce LDL-C $\geq$ 50% Ideal goal: LDL-C < 1.8 mmol/L (70 mg/dL)
<b>With subclinical atherosclerosis assessment</b>	<b>Advanced subclinical atherosclerosis</b> <i>Coronary:</i> A-Coronary artery calcium (CAC) score > 100 Agatston units, or > 75 <sup>th</sup> percentile for age and gender*  B-Computed tomography angiography (CTA) with obstructions > 50% or presence of non-obstructive plaques > one vessel.	Realistic goal: reduce $\geq$ 50% Ideal goal : LDL-C < 1.8 mmol/L (70 mg/dL)
<b>At presentation</b>	LDL -C >10 mmol/L (400 mg/dL) LDL-C >8.0 mmol/L (310 mg/dL) + one high risk condition LDL-C > 5 mmol/L (190 mg/dL) + two high risk conditions	Realistic goal: reduce $\geq$ 50% LDL-C Ideal goal: LDL-C < 2.5 mmol/L (100 mg/dL)

**Legend for table 1: High risk conditions:**

Older > 40 years old without treatment , smoking, male gender,

Lp(a)>50 mg/dL (75 nmol/L), low-HDL-C (<1mmol/L or 40 mg/dL),

hypertension,

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 rate  $< 60$  ml/min/1.73 m<sup>2</sup>,

and body mass index  $>30$  kg/m<sup>2</sup>.

\* MESA criteria ( <http://www.mesa-nhlbi.org/calcium/input.aspx>) accessed on March 21, 2016

**Table 2 Treatments approved for severe FH forms in adult patients using standard lipid lowering therapy who persist with uncontrolled lipid levels**

	<b>Mechanism of action</b>	<b>Dosage/frequency</b>	<b>Remarks</b>
Lipoprotein apheresis <sup>38</sup>	Extra-corporeal removal of pro atherogenic apolipoprotein B (apo B) containing lipoproteins. Reduces apo B, LDL, VLDL and Lp(a) concentrations.	1 session a week or every 2 weeks. Current apheresis methods temporarily reduce apo B containing lipoproteins including LDL, VLDL and Lp(a) by 60-80%.	Indications approved by the FDA for lipopheresis a) Functional FH homozygotes with >13 mmol/L) b) Functional FH heterozygotes with LDL-C >8.0 mmol/L c) Functional FH heterozygotes with LDL-C >5.0 mmol/L and documented coronary heart disease Values after 6 months of diet and maximum tolerated drug therapy.
Mipomersen <sup>13</sup>	Antisense oligonucleotide that binds to mRNA for apolipoprotein B blocking translation.	200 mg sc every week (160 mg if bodyweight <50 kg). Reduces LDL-C, apo B, and Lp(a) respectively by 25%, 27% and 31% in HoFH.	Approved for homozygous FH adults in the USA. Main side effects: injection site reactions 77%, flulike symptoms 29%, aminotransferase elevations > 3 x ULN in 12%. Increments in liver fat tend to stabilize with time and revert with drug suspension. Prescription following a REMS program.

Lomitapide <sup>14</sup>	Microsomal triglyceride transfer protein (MTP) inhibitor. Reduces the synthesis of VLDL and chylomicrons.	5-60 mg per oral/day (average clinical trial dose was 40 mg). The maintenance dose of lomitapide should be individualized. Reduces LDL-C, apo B, and triglycerides respectively by 50%, 49% and 45%.	Approved for homozygous FH adults in USA, Canada and Europe. Due to inhibition of fat absorption by the gut start a low-fat diet (<20% of energy from fat, and titrate dose based on safety/tolerability). Gastrointestinal (nausea, vomiting, bloating) side effects seen in 30% of patients. Fat soluble vitamins supplement should be instituted. Aminotransferase elevations > 3 x ULN in 33%. Increments in liver fat tend to stabilize with time and revert with drug suspension. Can be used in patients submitted to lipopheresis. Metabolized by CYP3A4 check for drug interaction. Maximal dose of atorvastatin should not be > 30 mg/day. In the USA prescription following a REMS program.
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Evolocumab <sup>10,55</sup>	Binds to plasma PCSK9, reducing endosomal degradation of the LDL receptor. Increases LDL clearance from plasma.	420 mg sc (approved dose for HoFH) every 4 weeks or 140 mg sc every 2 weeks.  Reduces LDL-C by 31% in HoFH vs. placebo. However response depends on the type of LDLR mutation (from no response to 40% LDL-C lowering depending if mutations null or defective)  Reduces LDL-C, apo B, and Lp(a) respectively by 60%, 49% and 30% in HeFH.	Approved for FH including HoFH in USA and Europe. Most frequent side reactions: nasopharyngitis 5-10%, headache 4%, injection site reactions 5-7% (all non different from placebo).
Alirocumab <sup>20</sup>	Binds to plasma PCSK9, reducing endosomal degradation of the LDL receptor. Increases LDL clearance from plasma.	75 mg sc up titrated to 150 mg sc every two weeks.  Reduces LDL-C, Apo B and Lp(a) respectively by 51-58%, 39-41% and 20-30%.	Approved for FH in USA and Europe. Most frequent side reactions: nasopharyngitis 11.2-12.6%, headache 4%, injection site reactions 11.4-12.4% (all non different from placebo).

**Legend for table 3: REMS (Risk Evaluation and Mitigation Strategy)**

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**Legend for Figure 1: Treatment algorithm for severe FH**

Legend for figure 1: Treatment based on refractoriness of treatment, on drug or procedure availability, reimbursement and approval by local regulatory agency.