

Title: The Continuing Challenge of Familial Hypercholesterolaemia

Editorial for “Prediction of Cardiovascular Risk in Patients with Familial Hypercholesterolaemia”

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Word Count: 1638

References: 21

Familial hypercholesterolaemia (FH) is a common genetic disorder of cholesterol metabolism. Mutations in key genes, namely *LDLR*, *PCSK9* and *Apo B* lead to disturbances in lipid regulation with affected individuals exhibiting a lifelong elevation of plasma LDL-C, a marked tendency to premature atherosclerosis and early coronary heart disease (CHD) events.^{1,2} With an autosomal dominant pattern of inheritance, only one copy of an abnormal gene is required to produce hyperlipidaemia and CHD risk, commonly known as heterozygous FH.

Unlike many genetic disorders, FH is eminently treatable, especially following the widespread availability of potent lipid lowering agents such as statins. Indeed, early and sustained therapy to lower LDL-C in FH patients can have a profound impact on retarding atherosclerosis development and preventing premature CHD. Despite this preventative benefit, FH still remains poorly recognised and under-treated.³ With the recent emergence of more potent therapies and new diagnostic and screening strategies, there are growing calls to raise awareness of FH across the world, and step up population level efforts to find affected individuals.^{2,3}

Risk Modelling & Cost Effectiveness

Population level screening, diagnostic testing and new treatments come at a cost and require substantial investment. At a time of financial austerity the cost-effectiveness and clinical value of any new intervention for identifying or treating FH, needs to be clearly demonstrated. While well-established methods and metrics exist for cost-effectiveness analyses, they commonly rely on robust modelling and projection of risk, which for FH has remained problematic.⁴

That patients with FH are at a risk of premature CAD is of course well known. For example, early studies estimated that men with heterozygous FH will have a 50% risk of developing CHD by the age of 60 years and women 30%,⁵ while a recent Norwegian study showed that the mean age of death in FH is 60 by which time 93% had cardiovascular disease.⁶ However, many such studies reporting on risk of CHD for FH have been conducted with highly selected populations, including patients at a particular stage in life, without accounting for the lifetime risk from high LDL since birth, or the variable extent and timing of past treatment especially statins. Importantly the impact of competing risks from traditional risk factors like obesity, hypertension and diabetes are also not frequently or fully accounted for.

In contrast, for non-FH populations, estimates of CHD risk are available from large prospective studies of unselected populations free from, or minimally susceptible to, bias. Risk equations derived from these data then permit accounting for population differences and adjustment for differing degrees of competing risk factors.⁷ Thereafter these equations can be incorporated into decision analysis models which systematically consider possible outcomes, to inform cost effectiveness analyses.⁴ Unfortunately, comparable risk equations are not available for FH populations due to the relative rarity of the condition. Direct use of non-FH risk equations would markedly underestimate risk for this group and render any cost effectiveness estimates unreliable.

Lifetime Risk for FH Patients

In this issue of the journal, Villa and colleagues have sought to address this challenge by first identifying the least biased population-based study reporting FH and CHD risk, a Danish study of 69K people.⁸ They then used those estimates to “adjust” existing risk equations for primary (Framingham) and secondary prevention (REACH 2012) to better reflect the greater risk of events FH patients have in comparison to non-FH patients.⁹ These equations were then incorporated into a decision analysis model using a population modelled on participants from a recent clinical trial of FH patients,¹⁰ to reflect prevalence and distribution of characteristics and risk factors as well as prior treatment rates and included scenarios whereby individuals had established CVD, no CVD or acute CVD (ACS, HF and stroke).

The study comes to the remarkable conclusion that, assuming all assumptions are valid, 10 year risk for FH patients is close to 47%, or in other words, almost every other FH patient would experience a CV event in the next 10 years, with risk being higher for older subjects and lower for those below 40. Even more remarkable is the finding that the predicted lifetime risk was as high as 88% for a first CV event, meaning that almost every FH patient will experience at least one CV event in their lifetime. Compared to a non-FH patient, an FH patient would thus have almost 4 times higher risk of CV events over a lifetime.⁹

As with any study such as this, multiple assumptions are needed, some of which may or may not impact the validity of the findings. For example it is assumed that the effect of traditional risk factors on CHD risk is independent of FH status, yet we know that diabetes is less prevalent among FH patients, while statin therapy itself is associated with diabetes risk and thus interactions may conceivably exist.¹¹ The validity and assumptions of the original population study which are used to adjust the risk estimates could also be questioned given that only partial data was available to make the diagnosis of FH, mostly from lipid levels and family history data while genetic mutation data for the same population was only available later and may have impacted findings.¹² However, even with such issues, and anticipation of future refinements to the approach, this study is still useful in providing a sense of the scale of lifetime risk for FH patients and the importance of better diagnosis and management of FH.

Challenges around diagnosis of FH

The primary challenge for FH remains the identification and diagnosis of cases so they can be offered early and aggressive therapy.³ The average worldwide prevalence of heterozygous FH was considered to be approximately 1 in 500, based on early studies and Hardy Weinberg estimates using homozygous FH prevalence.¹ However latest genetic epidemiological analysis and next generation sequencing data suggest the prevalence may in fact be closer to 1 in 200-250, more than double previous estimates.¹²⁻¹⁴ The higher prevalence however makes the scale of under diagnosis even worse with recent estimates indicating that barring a few notable exceptions, only 1% of cases have been diagnosed formally in most European countries based on revised prevalence estimates.¹⁵

Currently FH cases are diagnosed using clinical scoring criteria and/or DNA based analysis, mostly in an ad-hoc manner, either after a CHD event, routine health screen or a blood test highlighting an abnormally high cholesterol value. Cascade testing is a systematic approach to finding additional cases, by testing the relatives of confirmed FH patients and can be done through genetic mutation

analysis or through lipid levels. The approach is recommended by professional societies and has been successfully implemented in countries such as the Netherlands.³ However, finding the index cases themselves is the limiting factor for cascade testing. Formal national screening programs are a better option in this regard and the feasibility of child screening has been shown in Slovenia where all 5 year olds are tested for lipids with genetic testing for those with elevated levels.¹⁶ Expanding further, Wald et al examined an even more attractive reverse-cascade approach by testing 10,000 infants 1-2 years of age at the time of vaccination and (using a total cholesterol cut off of the 95th percentile) finding in total 40 affected children and at the same time 40 affected parents.¹⁷

However, such approaches are highly dependent on the threshold of LDL levels used for screening. Furthermore, genotyping and sequencing in large populations has demonstrated that only ~2% of people with elevated lipid levels have a genetic mutation for FH, illustrating the difficulty with only using lipid levels to diagnose or screen for FH.^{13, 14} In addition, 27% of FH mutation carriers have LDL levels <3.3mmol/L indicating the incomplete phenotypic penetrance of the genetic mutation, although carriage of an FH genetic mutation still elevates CHD risk for any given level of LDL compared to non-carriers.^{13, 14} These definition uncertainties, along with absence of proven long term benefit of cascade testing or screening, along with the extensive cost of infrastructure and resources needed to implement them, may partly explain the ongoing lack of progress in identifying FH in countries around the world.

Challenges around treating FH

Since the clinical complications of atherosclerosis occur prematurely, lifelong treatment, started as early as possible is needed to reduce the risk of future cardiovascular disease. Statin therapy in patients with heterozygous FH is highly effective and has been shown to lower atherosclerosis progression and also cardiovascular events.¹⁸ Statin use in children is also safe and effective, with guidelines advocating starting therapy at ages 8-10.¹⁹

However, many patients with confirmed or potential FH still do not achieve adequate LDL lowering.³ A recent study using electronic health record data, estimated that only 58% of those with an FH mutation were on statins and only than 46% of these achieved an LDL target of <1.8mmol/L.¹³ This may partly be due to suboptimal dosing, under-appreciation of risk by clinicians, treatment resistance or statin intolerance. Additional drug options include ezetimibe and more recently PCSK9 inhibition, with the latter able to reduce LDL levels by more than 60%.¹⁰ In non-FH patients PCSK9 inhibition has shown improvements in CV outcomes and atheroma regression, with an expectation of similar benefit for those with FH.²⁰ Thus with these and newer agents also emerging, barriers to better LDL control for FH patients will no longer be simply due to lack of available therapeutic options.

Ultimately, demonstration of the cost effectiveness and benefit of the diagnostic and screening strategies as well as novel therapies for FH will determine whether we will succeed in reducing the burden of CHD due to this condition. The work by Villa and colleagues highlights the high lifetime risk of FH patients, and will inform the ongoing scientific and policy discussions. On final related note, by using standard CV risk equations, this paper is also a gentle reminder that in our FH patients, in addition to treating the LDL, we should not forget to address the many other risk factors

we usually treat in non-FH patients, and to maintain a broader perspective on lifetime cardiovascular risk.²¹

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