Simplified algorithm to facilitate communication of familial hypercholesterolaemia

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Unmet challenge 1: effective LDL lowering in FH in addition to statins

A new treatment option for heterozygous FH (HeFH) is demonstrated in this issue of the journal. The results of the ODYSSEY FH I and FH II trials presented by John Kastelein and colleagues\textsuperscript{4} convincingly show that biweekly subcutaneous injections of the PCSK9-inhibiting antibody alirocumab reduced LDL-C in 735 patients with HeFH by 52\% compared with placebo. The LDL lowering was observed in addition to maximally tolerated lipid-lowering therapy. ODYSSEY FH I + II confirm the efficacy of anti-PCSK9 antibodies for the lowering of apolipoprotein B (apoB)-containing lipoproteins and good tolerability that now has been demonstrated with high homogeneity in different regions throughout the world, by different investigators, in different patient populations and importantly—using two different PCSK9 antibodies, namely alirocumab and evolocumab.\textsuperscript{5,6}

Is there a price to pay for such a dramatic reduction of LDL-C that is primarily mediated by a significant alteration of the regulation of the hepatic LDL receptors (LDL-Rs)? Aside from the expected minor increase of injection site reactions, the short-term (24-week) ODYSSEY FH I + II studies reported no safety concerns. These data are in agreement with the reported normal phenotype of individuals with genetically low PCSK9 serum concentrations.\textsuperscript{7} A theoretical concern of treatment with antibodies relates to immune responses, especially with long-term exposure. Although immune responses are less frequent with the use of fully human antibodies such as alirocumab or evolocumab, anti-antibody responses could potentially inhibit the efficacy or induce adverse reactions. Here, antidrug antibodies (ADAs) were detected in 5.5\% (FH I) and 8.6\% (FH II) of the patients allocated to alirocumab, and most of them were transient. Neutralizing antibodies were found in three patients. The authors report no correlation between the ADAs and LDL-C-lowering efficacy, or a specific safety pattern. However, long-term observations will be necessary to explore fully the risk–benefit ratio.

Are PCSK9 inhibitors effective in patients with FH that have defects in their LDL-Rs? This question is of interest since their primary mechanism of action is increasing the number of LDL-Rs on the surface of the hepatocytes. In >90\% of cases, HeFH is caused by mutations of the LDL-R and only infrequently (~5\%) by mutations of apoB or, in rare cases (~2\%) of PCSK9.\textsuperscript{8} Indeed, in individuals with homozygous FH, the LDL-lowering effect of anti-PCSK9 antibodies was absent in LDL-R-negative individuals and markedly diminished as the number of alleles associated with receptor-negative activity increased.\textsuperscript{8} ODYSSEY FH I and FH II provide important confirmation...
that anti-PCSK9 antibodies are effective in HeFH. In the RUTHERFORD studies, HeFH patients with receptor-negative mutations responded similarly to evolocumab to those with defective mutations or mutations in apoB. In fact, LDL-C lowering in RUTHERFORD was unrelated to the underlying genetic mutation. ODYSSEY FH I and FH II support the view that the LDL-C-lowering effect in HeFH depends mainly on up-regulation of the non-affected LDL-R. This is similar to statins which also work by indirectly increasing LDL-R activity and are effective in patients with HeFH. As a consequence, all patients with HeFH respond, and genetic testing is not needed to predict the treatment effect. Interestingly, and in contrast to LDL-C, anti-PCSK9 antibodies reduce lipoprotein (a) in homozygote LDL-R-negative individuals. It is therefore possible that hepatic effects of PCSK9 inhibition that are not related to the LDL-R and/or extrahepatic effects, e.g. in the intestine, could potentially contribute.

In summary, from the clinical perspective, both alirocumab and evolocumab are well tolerated and provide randomized evidence for very large reductions in LDL-C in addition to statins and ezetimibe in the high-risk patient population with HeFH.

**Unmet challenge 2: identification of patients with FH**

The vast majority of patients with HeFH remain undiagnosed. The prevalence is estimated at 1:200–1:500 for most European countries. Despite an up to 13-fold increased risk of chronic heart disease, only 1% are diagnosed in most countries. Different approaches including cascade, reverse-cascade, opportunistic, and universal screening have been shown to be both feasible and helpful in various settings. Why are we doing so poorly using these strategies? Clearly education and awareness need to be increased. It may be time to ‘de-mystify’ FH and to move FH out of the corner of the academic world into the arena of primary care.

An important step therefore is facilitating the communication on how to diagnose FH clinically. Genetic testing is the gold standard to diagnose FH, but it has considerable limitations. It is too expensive at present for many settings and therefore cannot be widely implemented. In addition, even with advanced technology, only 80% can be correctly diagnosed. Therefore, clinical scores such as the US MedPed Program, the Dutch Lipid Clinic Network, and

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**Figure 1** Simplified algorithm to detect and treat individuals with high LDL-associated genetic risk. CAD, coronary artery disease; FH, familial hypercholesterolaemia. Reprinted with kind permission from Klose G, Laufs U, März W, Windler E. Familial hypercholesterolemia: developments in diagnosis and treatment. Dtsch Arztebl Int 2014;111:523–529.
the score of the Simon Broome Register Group (which was used in ODYSSEY FH I + II) have been very helpful in the past. These clinical scores, however, are complicated and rely on skin manifestation of FH. However, a large number of patients with HeFH do not exhibit arcus lipoides, xanthomas, or any other cutaneous sign of FH. The scores leave the user with categories of ‘possible’ or ‘probable’ for the majority of patients. This is frustrating since the very reason for undertaking the time-consuming exercise of the score was the clinical suspicion of FH in the first place. Although the categorization ‘possible’ may be correct with respect to matching the result with genetic testing, it is not very helpful from a clinical point of view and we have to acknowledge the fact that outside the world of academia, lipid clinics, and specialists, these complex materials are hardly used.

Our perspective on the genetic determination of serum LDL concentrations has changed since the above-mentioned scores were developed. Mendelian randomization confirms LDL-C as a causal risk factor of atherosclerosis. Numerous sets of genetic data have become available recently that demonstrate a linear relationship between genetically altered LDL-C and cardiovascular risk. Large meta-analyses show that genetic predisposition is the major determinant of serum LDL concentrations. Gene variants or combinations of genes that lead to higher than average circulating levels of LDL are directly and ‘dose-dependently’ associated with increased risk. Furthermore, the exposure time to elevated LDL-C plays an important role with respect to cardiovascular risk. In that context it is important to identify patients with genetically determined elevated LDL-C and differentiate them from those subjects who only develop elevated LDL-C later in life. Most probably it is of secondary importance whether one single or several genetic mutations are clearly benefit from lipid lowering. This simplified approach has limitations. If the family history is not available or incorrect, the interpretation of an elevated LDL-C may be more difficult. However, this categorization ‘possible’ may be correct with respect to matching the result with genetic testing, it is not very helpful from a clinical point of view and we have to acknowledge the fact that outside the world of academia, lipid clinics, and specialists, these complex materials are hardly used.

How could the communication on the detection of HeFH be moved from complicated to straightforward? We suggest using a simple algorithm (Figure 2). The primary clinical aim is to detect individuals with high LDL-C. The second step is to understand whether the cause is primarily genetic. A genetic cause of high LDL-C indicates increased risk because of the long-term exposure whether the cause is primarily genetic. A genetic cause of high LDL-C indicates increased risk because of the long-term exposure whether the cause is primarily genetic. A genetic cause of high LDL-C indicates increased risk because of the long-term exposure whether the cause is primarily genetic. A genetic cause of high LDL-C indicates increased risk because of the long-term exposure whether the cause is primarily genetic. A genetic cause of high LDL-C indicates increased risk because of the long-term exposure whether the cause is primarily genetic. 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