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EDITORIAL COMMENT

Improving the Monitoring and Care of Patients With Familial Hypercholesterolemia*

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Familial hypercholesterolemia (FH) is an autosomal codominant disorder characterized by markedly elevated plasma concentrations of low-density lipoprotein (LDL) cholesterol, typically >190 mg/dl (>5 mmol/l) in adults (1-3). In most populations, ~1 in 300 individuals carries a single copy of a loss-of-function allele in the gene encoding the LDL receptor (*LDLR*) or another variant in a related protein, which underlies the heterozygous form of FH (HeFH) (1-3). Untreated affected individuals have a markedly increased risk of premature cardiovascular disease (CVD), especially coronary heart disease (CHD) and early mortality (1-3). Each of several widely used diagnostic criteria for HeFH requires the presence of elevated LDL cholesterol concentration; confidence in the diagnosis increases from "possible" to "probable" to "definite" with mounting corroborating evidence, such as characteristic clinical features (e.g., tendon xanthomas, xanthelasmas, or corneal arcus), family history, and a positive DNA test result (1-3).

Early diagnosis of HeFH leads to timely initiation of life-saving preventive measures, such as lifestyle intervention and a statin (1-3). In the pre-statin era, age-specific total and cardiovascular mortality in HeFH were log orders of magnitude greater than in the general population (4). Since then, these have been dramatically reduced, although not completely normalized with statin treatment (5). CVD prevention in HeFH is driven by reducing plasma LDL cholesterol; guidelines from professional societies often recommend targets for HeFH patients (1-3). However, the rationale for specific goals in HeFH is not derived from prospective, randomized clinical trial (RCT) evidence because such trials have not been performed in HeFH patients. Instead, specific absolute targets, such as an LDL level <100 mg/dl (<2.6 mmol/l) are extrapolated from guidelines for CVD risk reduction in the general population, at least from guidelines that still advocate LDL cholesterol targets (6,7).

Targets for high-risk HeFH patients are consistent with LDL cholesterol levels at which plaque stabilization or even regression of atherosclerosis are possible. However, there are logistical challenges in HeFH patients: because their baseline concentrations are so high, treated LDL cholesterol rarely reaches recommended target levels, even with high-potency statins and combination treatment. For instance, 1 study found that >80% of molecularly diagnosed and well-treated adult HeFH patients failed to reach an LDL cholesterol of <100 mg/dl (<2.6 mmol/l) (8).

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The challenges in treating HeFH patients to reach conventional LDL cholesterol target levels are further underscored in this issue of the *Journal* by Perez de Isla et al. (9). The multicenter, prospective SAFEHEART (SpAnish Familial HypErcHolEsterolemiA CohoRT) study has recruited 2,752 patients from Spain and their relatives older than 15 years of age with a genetic diagnosis of HeFH since 2004. Genetic diagnosis reduces confounding inherent in clinical diagnostic schemes that require detection of

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characteristic physical findings; the ability to detect such findings may vary between sites, according to clinical experience and acumen of the investigators. Although it has limitations (1-3), genetic testing theoretically provides a more uniform diagnostic standard for a registry like SAFEHEART that operates across multiple centers and clinics.

The SAFEHEART investigators followed 2,170 genotyped HeFH patients (mean age, 45 years and ~45% male) for a mean of 5.1 years. Approximately 13% had previous atherosclerotic CVD, approximately one-fourth actively smoked cigarettes, and ~4% had type 2 diabetes. Of >200 unique mutations mainly in the *LDLR* gene found in this cohort, approximately one-half were of the receptor-defective variety, whereas approximately one-third were of the more severe receptor-null variety. The investigators found that ~72% of HeFH patients were on maximal lipid-lowering therapy, as defined by "high-intensity statin" agents and doses (10). More than one-third of SAFEHEART patients also took ezetimibe, usually in combination with a high-intensity statin (9). Treated LDL cholesterol level at baseline was 163 mg/dl (4.2 mmol/l). At follow-up, LDL cholesterol level decreased by 16% to 137 mg/dl (3.5 mmol/l); this was associated with both a shift from atorvastatin to rosuvastatin as the primary foundational statin and an increase in ezetimibe use.

Despite the clinical improvement, the proportion of subjects achieving an LDL cholesterol level <100 mg/dl (<2.6 mmol/l) was low throughout the study, increasing from 4.7% at baseline to only 11.2% at follow-up. Predictors of goal attainment included the presence of diabetes, the absence of previous atherosclerotic CVD, the use of ezetimibe, and the presence of a receptor-defective mutation (9). Better goal attainment in HeFH patients with type 2 diabetes suggests greater motivation and adherence in this very high-risk subgroup. Because ezetimibe further reduces LDL cholesterol (11), it follows that patients taking a statin plus ezetimibe were more likely to reach their goal. Better goal attainment when CVD was absent suggests that this subgroup had a less severe and thus perhaps more easily treated HeFH phenotype. Similarly, individuals with receptor-defective mutations have a somewhat less severe HeFH phenotype than those with receptor-null mutations (1); assuming their baseline LDL cholesterol levels were lower, their chances of goal attainment would be better.

What are the implications of SAFEHEART's main findings? First, SAFEHEART confirms the value of a national HeFH registry, which permits assessment of demographic and defining features along with objective monitoring of performance and outcomes (12). Second, the very low rate of LDL cholesterol goal attainment in the context of admirable deployment of traditional lipid-lowering therapy suggests either that standard target levels are unsuitable in HeFH or that new strategies are required to help HeFH patients attain recommended goals.

It is beyond the scope of this paper to reopen the debate on the appropriateness of target LDL cholesterol levels (6,7,10). However, most would likely agree that tracking LDL cholesterol in HeFH patients is reasonable because the main risk to health and longevity revolves around disturbed LDL cholesterol, despite the absence of RCTs specifically testing the treat-to-target hypothesis in this population. So assuming that a "fire-and-forget" treatment strategy represents an inadequate standard of care in HeFH and that some ongoing LDL cholesterol monitoring is appropriate, what is a reasonable target level? As far as we know, there is nothing genetically distinctive about the arteries of HeFH patients; they respond in the same way to atherogenic stressors as arteries in the rest of the population except that the integrated burden of injury from high LDL is much greater, having started from the moment of conception. So it is not outrageous to suggest that the same absolute LDL cholesterol target levels that apply to the general high-risk population of cardiology patients should also apply to high-risk HeFH patients, with the usual caveats about the limitations of such targets (6,7).

What can be done to improve the low rate of attaining an absolute LDL cholesterol target level with conventional lipid-lowering therapy in HeFH, as shown by SAFEHEART? For an average HeFH patient, this would require >70% reduction of LDL cholesterol from baseline. Reductions of this magnitude are usually beyond the capability of the traditional treatment armamentarium (11). In this regard, the recently approved monoclonal antibody inhibitors of proprotein convertase subtilisin kexin 9 (PSCK9) would seem to be ideal agents for HeFH patients. Indeed, short-term clinical trials with alirocumab and evolocumab conducted in HeFH patients indicate that this is the case.

For instance, when alirocumab was added to conventional lipid-lowering treatment in HeFH patients, the mean LDL cholesterol level decreased from 145 mg/dl (3.7 mmol/l) to 71 mg/dl (1.8 mmol/l) at 24 weeks (48.8% reduction vs. placebo; $p < 0.0001$) (13). At various pre-specified time points, HeFH patients randomized to alirocumab achieved LDL cholesterol <70 mg/dl (<1.8 mmol/l) at rates between 60% and 81% compared with 1% to 11% for patients randomized to placebo (all p values <0.0001). Similarly, compared with placebo, when evolocumab was added to

conventional lipid-lowering treatment in HeFH patients, the mean LDL cholesterol level decreased from 147 mg/dl (3.8 mmol/l) to 66 mg/dl (1.7 mmol/l) at 12 weeks (59.2% reduction vs. placebo, $p < 0.0001$) (14). On 2 different dosing regimens, HeFH patients randomized to evolocumab achieved an LDL cholesterol level <70 mg/dl (<1.8 mmol/l) at rates between 63% and 68% compared with 1% to 2% of patients randomized to placebo (all p values <0.0001) (14).

Therefore, PCSK9 inhibitors might satisfy the unmet need for additional LDL cholesterol reduction in HeFH patients seen in the SAFEHEART. Indeed, current indications for these agents include HeFH patients who require additional lipid lowering. However, a couple of final issues are worth considering. First, although meta-analyses of small short-term studies with PCSK9 inhibitors show reduced all-cause mortality with ~1 year of treatment (odds ratio: 0.43, 95% confidence interval: 0.22 to 0.82, $p = 0.01$), with apparently no heterogeneity between studies that did or did not enroll HeFH patients (15), we still await the results of definitive large-scale, long-term RCTs of cardiovascular outcomes in the general cardiology population. Second, a recent cost-benefit analysis using usual assumptions showed that the number of HeFH patients needed to treat over 5 years to prevent 1 major cardiovascular event with a PCSK9 inhibitor was 28 (16). With a yearly price tag of ~$14,500, the cost per quality-adjusted life-year gained was ~$290,000 by treating a HeFH with a PCSK9 inhibitor, which is high by any yardstick (16). By reducing the cost of these agents by >60%, the cost per quality-adjusted life-year gained in HeFH is lowered to <$100,000, which is within the range considered by some third-party payers to represent "good value" compared with other widely reimbursed therapies such as hemodialysis (16). As PCSK9 inhibitors enter the clinical mainstream, national registries such as the SAFEHEART will allow for monitoring of their use, efficacy, and cost-benefit in HeFH.

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