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EDITORIAL COMMENT

Hypercholesterolemia Among Premature Infarcts

Time to Start the Clock of Familial Hypercholesterolemia Assessment*

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Benn et al. (1) have shown recently that the prevalence of familial hypercholesterolemia (FH) is about 1:250 individuals in an unselected general population, in contrast to prior estimates of 1:500. Since then, many reports from around the world have confirmed this finding (2). This makes FH the most common autosomal genetic disorder affecting humans, resulting in premature cardiovascular disease (CVD) through lifelong elevated low-density lipoprotein cholesterol (LDL-C) levels. FH is fairly easy to diagnose; either upon the identification of mutations in the culprit genes (*LDLR, APOB,* and *PCSK9*) or by using a scoring system, such as the Dutch Lipid Clinic Network (DLCN) criteria. Current guidelines provide a Class 1 recommendation for LDL-C lowering in FH patients (3,4). The evidence base for lowering LDL-C in FH per se is less robust, as few true FH patients have been recruited into randomized controlled trials. However, both post hoc analyses of trial data (5) and observational studies have consistently shown a clinical benefit of statin therapy in patients with FH (6). Unfortunately, an enormous gap exists between clinical science and clinical practice, because FH remains underdiagnosed and undertreated in most countries (7), likely resulting in preventable long-term morbidity and mortality in FH patients. For that reason, the mantra for FH is "early detection and early treatment."

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In this regard, the study by Singh et al. (8) in this issue of the *Journal* contributes as the authors attempted to calculate the prevalence of FH among young survivors of a first myocardial infarction (MI) before age 50 years between 2000 and 2016. The authors describe the management and care of these individuals before and after the index MI event through record linkage within the PARTNERS YOUNG MI Registry. The authors conclude that FH is common (affecting approximately 1:10 of young MI survivors), that around one-half are not on statins prior to their MI, and that LDL-C goal attainment of <70 mg/dl is poor. The findings merit closer attention.

Autosomal dominant FH has a defined genetic basis with associated physical manifestations, salient features in the family history, in addition to the high LDL-C levels. While some have attempted to simplify the definition to one based on LDL-C levels alone (9), this is potentially misleading as hypercholesterolemia per se often has a polygenic basis (10,11) or even reflects elevated Lp(a) levels (12). Hence, the validity of the definition of FH is critical to the main conclusion

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of the current study. Singh et al. (8) use the DLCN criteria to estimate a prevalence of 9%, which is very similar to the numbers reported earlier from other regions of the world (13–16). The DLCN uses points to identify the likelihood of FH, with those having 6 to 7 points being considered as probable and those with 8 points or more as definite FH. In this study, everyone would have started with 2 points for premature MI. This may artificially lead to overestimating the number of FH cases in this cohort (14). Furthermore, none of these patients were validated against the gold standard of genetic testing for FH. In short, the true prevalence of FH in this group is likely to be considerably <1:10. Indeed, unbiased estimates suggest that insulin resistance, diabetes, and smoking contribute to a greater extent to the risk for young MI at population level (17). This is supported by the high prevalence of diabetes, smoking, and hypertension both among the so called "FH cohort" and the non-FH patients in the present study, a fact that is not usually observed in unselected longitudinal studies of FH. Most likely, the population defined by Singh et al. (8) as having FH, have primary hypercholesterolemia, consisting of some with true autosomal dominant FH, others with polygenic hypercholesterolemia, and some with elevated Lp(a).

Singh et al. (8) report that 57.2% of the FH patients (and 10.4% of the non-FH patients) were on statin therapy prior to their MI. The difference in statin prescribing between the 2 groups is unsurprising given that elevated LDL-C >190 mg/dl is a primary indication for statins irrespective of cause (4). Moreover, LDL-C levels were determined at 1 year after discharge in 650 patients with a 77% decrease in LDL-C among FH and 39% among non-FH compared with LDL-C levels at MI occurrence, reflecting the greater use of high-intensity statins in the FH group. The authors suggest that 82.2% of FH patients did not reach the recommended LDL-C target of <70 mg/dl after 1 year. As more than 50% of FH patients were on a statin at baseline, the authors estimated through back calculation untreated LDL-C levels, which were then in turn used in the DLNC algorithm to define FH. These calculated LDL-C levels were then used to determine whether treatment goals were achieved and is thus akin to a self-fulfilling prophecy, whereby goal attainment in FH is defined from variables used to create the FH cohort in the first place.

The observation that there were no mortality differences between FH and non-FH patients makes it hard to justify the notion that the FH patients in this cohort should have been given further add-on lipid-lowering therapies, such as ezetimibe and PCSK9 inhibitors, routinely. Any conclusion on this, however, has to be drawn with great care, because it was stated by the authors that this study was probably underpowered to perform a sufficient survival analysis.

In summary, the present study in our opinion highlights the fact that hypercholesterolemia is common in survivors of premature MI. Among such patients, an assessment of the likelihood of FH should be conducted in a pre-discharge hospital setting, using a validated tool such as the DLNC rather than LDL-C levels alone, which are less specific to diagnose FH. In addition, a single Lp(a) measurement is needed. Among those who are probable or definite FH, genetic testing should be offered to assess whether autosomal dominant FH is present, as this will open the door to cascade testing and treatment of FH.

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