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EDITORIAL COMMENT

Family History and Lipoprotein(a) Contribute Independently to Risk Assessment and Clinical Management*

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Among the frequently encountered dilemmas in the management of lipoprotein disorders are in whom and at what age to introduce lipid-lowering medication. This is particularly the case in people whose 10-year atherosclerotic cardiovascular disease (ASCVD) risk has not reached the threshold for the introduction of statin therapy (7.5% to 10.0%), but who have an adverse family history (FHx). When the low-density lipoprotein (LDL) cholesterol exceeds 190 mg/dl, statin treatment is indicated, regardless of calculated risk even in young people (1) and, for those in whom the diagnosis of heterozygous familial hypercholesterolemia (HeFH) is suspected, DNA testing should be available (2). But, people with LDL cholesterol <190 mg/dl and 10-year ASCVD risk <10% are not immune to ASCVD events. If 10-year ASCVD risk is predicted to be, say 5%, at age 45 years, why wait until it reaches 10% with advancing age? The majority of such people will, of course, not experience ASCVD events during the wait: their true risk, had we but known, was thus 0. However, a small but finite number will not be so lucky, and their ASCVD events may have been preventable. They may be identifiable by the presence of additional risk factors not included in the algorithm for ASCVD risk assessment, which will thus underestimate risk. Caution is needed, however, because inclusion of too many candidate risk factors in risk prediction algorithms will not necessarily improve their accuracy, but may erode the apparent contribution of others for which intervention is possible (cholesterol, blood pressure, and smoking). Current guidelines therefore emphasize the importance of considering 2 additional factors, FHx and lipoprotein(a) [Lp(a)], but stop short of actually including them in the risk-estimating algorithm (3).

SEE PAGE 781

In this issue of the *Journal*, Mehta et al. (4) provide evidence for FHx and Lp(a) as additional risk factors and support the inclusion of both in future iterations of ASCVD risk engines. The novelty of the report is that both FHx and Lp(a) were measured in the same cohorts. Lp(a) concentration, which is substantially genetically determined, is known to be associated with ASCVD and with a positive FHx of premature ASCVD, but studies including both as covariates have been too small to be sure whether they acted in concert or simply overlapped in their association with ASCVD (5).

FHx of premature ASCVD should not be regarded as representing simply the genetic contribution to risk; it is a complicated amalgam of genetic and acquired factors. With the exceptions of HeFH and Lp(a), which both have a monogenic pattern of inheritance, most genes contribute to atherogenesis in a polygenic manner (6). Several, which acting alone would have little, if any, discernible effect, must be inherited in combination to contribute substantially to ASCVD risk. Sometimes, an adverse cluster of atherogenic genes are not separated at meiosis, and a similar

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combination can thus be present in first-degree relatives. Dominant inheritance can then be mimicked, as occurred in earlier descriptions of familial combined hyperlipidemia (7). In yet other individuals, FHx underestimates the genetic contribution to risk, because atherogenic genes from both sides of the family may be combined in them, but in neither the distaff nor the agnate side are their number sufficient to cause premature ASCVD. On the other hand, FHx of premature ASCVD may arise from nurture, habits such as smoking, aversion to exercise, and overnutrition being acquired from growing up in the same family. FHx may thus be somewhat blunt-edged, but reckoning with imponderables rather than precise mathematical quotients is commonplace in clinical practice. What age defines premature ASCVD and whether to include siblings requires clarification. Mehta et al. (4) report 2 cohorts each with a different definition of FHx. In 1 myocardial infarction before the paternal age of 55 years or the maternal age of 60 years was regarded as FHx, whereas in the other cohort, FHx was considered myocardial infarction in male and female first-degree relatives before they were age 50 or 55 years, respectively. Hypothetically, sibling history is important in exposing a polygenic trait (when genes contribute from both sides of the family), but it depends more on the number of siblings and the age of your patient than limiting FHx to parents.

There is currently disagreement about whether FHx of premature ASCVD should be the main indication for measuring Lp(a) or whether everyone should have it measured at least once (1,8,9). The report from Mehta et al. (4) would suggest the latter. The current position in the United States regarding Lp(a) is that Lp(a) ≥50 mg/dl constitutes a risk-enhancing factor (1). In Britain, it has been proposed that when Lp(a) is >40 mg/dl, desirable non-high-density lipoprotein cholesterol should be <100 mg/dl (8). In European guidance, a Mendelian randomization study (10) has been highly influential, leading to the suggestion that people with Lp(a) levels >180 mg/dl have an increased lifetime risk of ASCVD similar to that in HeFH, and that they are twice as prevalent as HeFH (9). Certainly, in any patient in whom a possible diagnosis of HeFH is sought, Lp(a) should be measured, because a high level constitutes greater ASCVD risk whether ultimately HeFH is confirmed or the hypercholesterolemia proves to be polygenic (11,12).

The clinical management of raised Lp(a) is to lower LDL cholesterol, non–high-density lipoprotein cholesterol, or better, apolipoprotein B to an appropriate target depending on other risk-determining factors (1,8,9). This is usually accomplished with statins, although neither they nor ezetimibe lower Lp(a). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors do, however, decrease Lp(a), and in 1 trial, when added to statin treatment, benefit was greater in participants whose Lp(a) was above average (13). Monoclonal antibody PCSK9 inhibitors are likely to remain too expensive for any but the highest-risk patients, but RNA interfering technologies may provide more cost-effective alternatives either acting on PCSK9 or directly on apolipoprotein(a) synthesis (14). Increased Lp(a) associated with renal dysfunction can be reduced by transplantation, but there have been no trials of specific intervention (15). Recently, it was predicted from Mendelian randomization findings that a decrease in Lp(a) of 66 mg/dl would reduce ASCVD incidence by about one-fifth (16). The hazard ratio for ASCVD of 1.25 when comparing the upper and lower quintiles of Lp(a) in the study by Mehta et al. (4) provides a similar expectation.

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