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Editorial

Finding the Familial Hypercholesterolemia Needle in Acute Coronary Syndrome: The Haystack Is Smaller Than You Think

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See article by Kramer et al., pages 1322–1331 of this issue.

Familial hypercholesterolemia (FH), in its heterozygous form, is considered to be the most common autosomal genetic disorder in humans, with a prevalence in the general population of 0.4%, or 1 in 250.[1] Through genetic mutations in proteins ultimately involved in low-density lipoprotein (LDL)–cholesterol production or regulation, FH results in a lifelong increase in LDL-cholesterol concentrations, leading to a multifold increase in the risk of atherosclerotic cardiovascular disease (ASCVD), particularly with premature onset. Statins are generally as effective at LDL lowering in patients with FH as in the general ASCVD population, where their benefits on ASCVD outcomes and mortality are firmly established. Despite the availability of genetic testing and validated diagnostic algorithms, barely 10% of FH cases have been identified worldwide.[2] As such, there remains an incredible opportunity to better identify (and manage) patients with FH to prevent future events.

To this end, attention has turned to patients presenting with acute coronary syndromes (ACS), particularly at a young age, as an enriched source of FH cases.[3] Although such studies have generally demonstrated a higher FH prevalence than in the general population, they have been limited by size, geographic distribution, design restrictions, and non-standardized approaches to FH diagnosis. This has resulted in an imprecise estimate of the actual prevalence of FH in patients with ACS.

The study in this issue of the *Journal* by Kramer et al.[4] goes a long way to refining that imprecision and offers direction for the future. The authors performed a rigorous and well designed meta-analysis of 22 observational studies estimating the prevalence of FH in 31,436 patients with ACS from around the world. They identified an overall FH prevalence of 4.7%, more than 10-fold higher than in the general population. Confirming internal consistency, this prevalence rose to 7.3% in patients with ACS $\leq$ 60 years of age, and even further to 13.7% in those $\leq$ 45 years.

A number of the individual studies relied on genetic testing to identify FH, whereas others used validated algorithms such as the Dutch Lipid Clinic Network (DLCN) or Simon-Broome (SB) criteria or combinations thereof. In those studies using the most rigorous DNA-based identification of FH, the prevalence was 5.0%, very similar to the overall 4.7% prevalence. This suggests that reliance on diagnostic algorithms, rather than genetic diagnosis, did not unduly overestimate the true prevalence.

Kramer et al.'s meta-analysis has some major strengths that should lead us to agree with and act on their conclusions. The authors restricted their search to studies that used validated methods for FH diagnosis, rather than including studies that estimated FH prevalence based on cholesterol levels alone. They limited the study population to ACS patients (as opposed to stable ASCVD), and they included studies from around the world. Importantly, they did not restrict their studies to patients with premature ACS, which would have likely resulted in an overestimate of the true FH prevalence. In addition to the internal consistency of FH prevalence between DNA-based and clinical diagnostic algorithms and the increasing prevalence with decreasing age, they also showed a similar FH prevalence between sexes (5.5% for men and 5.7% for women). The criterion-standard DNA-based prevalence of FH in this population was 5.0%. Some have argued that only DNA-based methods should be used, owing to potential error with clinical algorithms. However, in this meta-analysis, the prevalence of FH was 5.5% with the use of the DLCN criteria and 7.4% with the use of the SB criteria, suggesting that both algorithms yielded results similar to those of DNA-based diagnosis. The way that the authors designed their meta-analysis would, if anything, have led to a biased underestimate of the true prevalence of FH in patients with ACS.

The authors can hardly be faulted for any major limitations in their analysis and findings. One area warranting further

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evaluation relates to concomitant ASCVD risk factors, such as diabetes, hypertension, and smoking, which are known to overcontribute to risk in younger populations. In contrast, younger patients with FH, even with ASCVD, often have fewer additional risk factors. It is possible that some of the patients identified as having FH may have actually had premature ACS due to polygenic hypercholesterolemia coupled with other ASCVD risk factors. However, this potential bias is minimized by the observation of similar FH regardless of genetic testing versus clinical algorithms. In addition, elevated lipoprotein(a) levels occur in about 10% of the population, contributing to higher LDL-cholesterol concentrations and to premature ACS, and as such they could falsely elevate the perceived prevalence of FH.[5] Lipoprotein(a) levels were not included in this meta-analysis. The validity of any estimate of FH prevalence is highly dependent on factoring in both lipoprotein(a) and polygenic hypercholesterolemia as contributors to risk.

Finally, we now have a validated Canadian definition of FH,[6] and it would be interesting to apply this definition to the large sample size in Kramer et al.'s meta-analysis. This would allow further validation of the Canadian definition against DNA-based diagnosis as well as against DLCN and SB criteria.

FH in all respects is an ideal target for widespread or even universal screening. It is a reasonably prevalent disorder in the general population (1 in 250), and is associated with a 10−20-fold increase in ASCVD risk, much of which is silent until a catastrophic event occurs, such as myocardial infarction, ischemic stroke, or sudden death. Its clinical suspicion is rooted in a commonly available and inexpensive blood test (LDL-cholesterol), for which inexpensive and remarkably safe treatments (statins) are available that have been shown to substantially reduce the risk of ASCVD events. With the recent introduction of PCSK9 inhibitors, monoclonal antibodies that provide substantial additional LDL-cholesterol and risk reduction when added to statins, even more FH patients can be effectively treated. Furthermore, although genetic testing is not mandated for a diagnosis of FH, the cost and availability of such testing is gradually improving. It is no doubt frustrating, then, that more than 90% of FH cases remain undiagnosed. Better identification of FH patients would not only improve their care, but also provide the opportunity for cascade screening of their family members to identify further cases and institute treatment before the onset of ASCVD. Universal screening in children, with reverse cascade screening of parents, has also proven to be a reasonable approach. However, universal screening, at least in Canada, still seems to be a pipe dream.

Therefore, we turn to opportunistic screening, limiting our efforts to patients with the highest ASCVD risk: those presenting with ACS. One could consider this population as the "low-hanging fruit" for FH identification, especially in those with premature ACS, where the prevalence of FH can approach 7%-14%. Based on Kramer et al.'s results, one could argue that all ACS patients should be screened for FH during the in-hospital phase, either with the use of DNA-based techniques or, more likely, through the application of validated clinical algorithms. This would also likely require a concomitant measurement of lipoprotein(a). Those with probable or definite FH could then be referred after hospitalization to specialized lipid clinics for counselling, genetic testing, cascade screening, and, of course, intensive LDL-cholesterol lowering. However simple this may sound, there are considerable challenges to such an approach. In the current era of limited resources, clinicians are pressured to discharge ACS patients as soon as possible, limiting the amount of time available that can be dedicated to suspecting and confirming FH. This is compounded by the fact that those precious few days in hospital for an ACS patient are fraught with the activity of coronary angiography, revascularization, decisions around antithrombotic therapies and bleeding risk assessments, and management of other ASCVD risk factors, to name only a few challenges. At the very least, clinicians managing patients with ACS must become more aware of the heightened prevalence of FH, and must at least keep suspicion of FH on their radar. Patients with suspected FH could be either referred at discharge to specialized clinics for verification of FH or highlighted in the hospital discharge summary for suitable follow-up in the outpatient setting.

Cardiologists have often said that identifying FH in their practices is like finding a needle in a haystack. In the case of patients with ACS, that haystack is a lot smaller than we thought.

Disclosures

The author has no conflicts of interest to disclose.

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