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Editorial

Low Rates of Identification and Treatment of Familial Hypercholesterolemia in France and Elsewhere: A Call for Universal Screening

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See article by Bérard et al., pages 744–752 of this issue.

Familial hypercholesterolemia (FH) is among the most important causes of premature cardiovascular disease, but it is underdiagnosed and undertreated worldwide.[1] National efforts to define the prevalence and treatment patterns of FH are essential to gauge global progress in managing this condition. In the current issue of the *Journal*, Bérard and colleagues[2] present the first analysis of the prevalence and management of FH in France. One of the key findings from this report is their estimate of the frequency of heterozygous FH in France as 1:120, higher than in many other countries. However, this estimate may be influenced by the use of imputation of baseline low-density lipoprotein cholesterol (LDL-C) in patients already receiving treatment.[3] By using a fixed conversion for baseline LDL-C, their estimate of prevalence was approximately 1:250, similar to the prevalence in most other countries.[4]

Despite this high prevalence, they find very low rates of identification of cases and inadequate treatment to currently recommended lipid targets when identified. Similar patterns have been observed in other parts of the world, including in Canada, although data from Canada suggest somewhat better treatment of lipids in these patients.[5] The LDL-lowering achieved by patients in the French study may be a reflection of the time of derivation of the data, between 1995 and 2005, when recommended targets were less aggressive and before high-intensity statins and ezetimibe were as widely used.

The low rate of identification of cases and low achievement of recommended treatment targets for FH in France is ascribed by the authors to being potentially related to the perception, including among French physicians, that the French are somehow uniquely protected against development of ischemic vascular disease—the so-called French paradox.[6] Although this is a potential component of the inertia in screening for and managing FH, similar low rates of identification and urgency of treatment of FH are unfortunately still the case in many regions of the world.

There are multiple barriers to the diagnosis and treatment of FH. These include a persistent lack of recognition by treating physicians and the general population of when the cause of elevated cholesterol is genetic as opposed to lifestyle related, uncertainty regarding the optimal timing to initiate treatment when FH is identified, and what targets to aim for. Other barriers are the lack of awareness and acceptance that elevated LDL and other atherogenic particles (together reflected in the non–high-density lipoprotein cholesterol level) are directly causal in atherogenesis.

The discovery that loss-of-function mutations in proprotein convertase subtilisin/kexin type 9 lead to chronic lowering of LDL-C and a marked reduction in coronary heart disease events over a 15-year follow-up period[7] was a landmark in underlining the benefit of lowering LDL-C from an early age. This finding greatly informed our approach regarding when to initiate lifelong treatment of FH, with a shift from the previous pattern of starting treatment at a largely arbitrary age in adulthood, to initiating treatment at a much younger age, based on the understanding that cumulative LDL-C exposure is a major driver of the atherosclerotic risk in FH. Based on these findings, as well as studies showing the safety and efficacy of statin therapy in children with FH such as the Hyper**c**holesterolaemia in C**h**ildren and **A**dolescents Taking **R**osuvastatin **O**pe**n** Label (CHARON) trial,[8,9] current guidelines for the treatment of FH recommend screening for the disease and initiating statin therapy between the ages of 8 and 10 years.[10]

All of this points to the question of how we effectively identify FH in patients early in life so that treatment can be initiated and the risk of premature coronary heart disease[11] can be brought down closer to that of individuals with normal LDL-C levels. The current Canadian Cardiovascular Society Position Statement on FH continues to recommend cascade screening of first-degree relatives of individuals with diagnosed FH as the primary means to increase identification of affected individuals.[10] This approach, although also promoted in many other parts of world, is dependent on the

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effective identification of index cases and the willingness of family members to be screened.[10] Therefore, family-based screening is most effective when coupled with population-based screening to provide a source of new index cases. The same position statement also made the recommendation that universal cholesterol level screening be considered for detection of FH in children, with reverse cascade screening of parents when warranted.[10] The latter was considered a weak recommendation, based on moderate-quality evidence and in light of the systematic challenges to instituting such a program. However, universal screening of children has been shown to be possible and effective, for instance when piggy-backed onto programs such as those for routine childhood immunizations.[12] With mounting evidence of the under-recognition and undertreatment of patients with FH worldwide, the time is ripe for Canada to take the bold move of instituting universal cascade screening for FH. Such a program would need to be combined with increased education of the public and physicians that very high cholesterol is not based on lifestyle choices, that it carries a very high risk of premature atherosclerosis and death, and that early and aggressive treatment indeed makes a difference.

Disclosures

G.A.F. is a member of the advisory board for Akcea Pharmaceuticals. L.R.B. has served on advisory boards for Amgen and Sanofi.

References

1. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-90a.
2. Bérard E, Bongard V, Haas B, et al. Prevalence and treatment of familial hypercholesterolemia in France. Can J Cardiol 2019;35:744-52.
3. Ruel I, Aljenedil S, Sadri I, et al. Imputation of baseline LDL cholesterol concentration in patients with familial hypercholesterolemia on statins or ezetimibe. Clin Chem 2018;64:355-62.
4. Akioyamen LE, Genest J, Shan SD, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open 2017;7:e016461.
5. Brunham LR, Cermakova L, Lee T, et al. Contemporary trends in the management and outcomes of patients with familial hypercholesterolemia in Canada: a prospective observational study. Can J Cardiol 2017;33:385-92.
6. Ferrieres J. The French paradox: lessons for other countries. Heart 2004;90:107-11.
7. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264-72.
8. Braamskamp M, Langslet G, McCrindle BW, et al. Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: results from the CHARON study. J Clin Lipidol 2015;9:741-50.
9. Braamskamp M, Langslet G, McCrindle BW, et al. Effect of rosuvastatin on carotid intima-media thickness in children with heterozygous familial hypercholesterolemia: the CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). Circulation 2017;136:359-66.
10. Brunham LR, Ruel I, Aljenedil S, et al. Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018. Can J Cardiol 2018;34:1553-63.
11. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol 2016;67:2578-89.
12. Wald DS, Bestwick JP, Morris JK, et al. Child-parent familial hypercholesterolemia screening in primary care. N Engl J Med 2016;375:1628-37.