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Editorial

Very high LDL cholesterol: The power of zero passes another test

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In the current issue of *Atherosclerosis,* Sandesara et al. [1] shed additional light on the understanding of risk in individuals with very high LDL-C and no previous cardiovascular event identified in the Multiethnic Study of Atherosclerosis (MESA). Primary prevention strategies to reduce cardiovascular risk are mostly based on non-pharmacologic lifestyle modifications and pharmacologic management of individual risk factors such as hypertension, diabetes and, most importantly, hypercholesterolemia. However, the objective of those prevention strategies is the reduction of cardiovascular events and mortality, not the sole change in values of biomarkers, such as LDL-C levels. Thus, all guidelines on risk stratification recommend the estimation of individual cardiovascular risk using some validated tool to define the use of lipid lowering medications [2].

Although most international guidelines still recommend a combination of risk estimation and LDL-C levels to define the need and intensity of pharmacologic treatment of inadequate LDL-C levels, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines have not implemented this approach since 2013 [3]. The reasons for this decision have been previously detailed but can be summarized as follows: 1. There is no evidence that the efficacy of statins to reduce cardiovascular risk is variable according to baseline LDL-C as the relative risk reduction is fairly constant irrespective of LDL-C levels and the absolute risk reduction is dependent only on absolute risk [4]; 2. Most primary prevention studies used fixed statin doses and the evidence to support a dose adjustment according to LDL-C level is scant; 3. There is no evidence that reaching exceedingly low LDL-C levels are associated with any increase in risk of adverse cardiovascular or non-cardiovascular events [5,6].

However, there is one clear exception. Even according to the latest ACC/AAHA guidelines update, those with severe hypercholesteremia, LDL-C levels > 190 mg/dL or 4.9mmol/L are deemed to be at such high risk that pharmacologic treatment should be considered irrespective of the estimated individual risk [3]. In fact, the recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines have specifically classified them as “high risk”, with an LDL goal of < 70 mg/dl (0.8 mmol/L) [7], which is unlikely to be achieved without additional non-statin agents such as PCSK9 inhibitors. The need to be aggressive in this subgroup is based on two considerations. First, the concept that a lifetime exposure to very high LDL-C levels leads to an exceedingly high life-time cardiovascular risk that might not be fully captured by traditional risk calculators. Second, this cut off can be used as an initial screening to identify individuals with familial hypercholesterolemia (FH), an autosomal dominant disease affecting 1/250 individuals and associated with a substantial increase in cardiovascular risk. However, this strategy also assumes that those individuals with very high LDL-C are a homogeneous high-risk population that is more likely to benefit from aggressive treatment irrespective of their calculated risk, despite the lack of evidence to support this. In fact, recent studies suggest that coronary atherosclerosis is not a simple function of lipid levels but a multifactorial disease. Blankstein et al. reported that nearly 1 in 2 individuals with ‘normal’ LDL-C have coronary atherosclerotic disease as measured by coronary artery calcium (CAC) testing [8] and conversely we have shown that even among those with genetically confirmed FH, nearly half show no detectable CAC and appear to have favorable intermediate term prognosis [9].

Thus, this raises the question if we should treat all subjects with very high LDL-C aggressively, as recommended in the ESC/EAS guidelines update or whether this population could benefit from additional risk stratification with tools such as CAC to guide pharmacological treatment. Most importantly, can the favorable prognosis of the “power of zero” calcium score observed in our intermediate term follow-up study of relatively young FH patients be extrapolated to severe hypercholesteremic patients (> 190mg/dL) in the general population on a longer follow-up? Sandesara et al. [1] evaluated the presence of CAC as well its prognostic implication in individuals with severe hypercholesterolemia in MESA. The first interesting aspect worth noting is its relatively low prevalence, only 4% of the entire MESA study population was estimated to have a treatment naïve LDL-C > 190mg/dL. Second, though it may seem surprising, a substantial proportion of individuals (37%) presented with a CAC score of zero at a mean age of 63(± 9) years, a prevalence of subclinical atherosclerosis comparable to the overall MESA cohort, despite the very high LDL-C levels. Moreover, in this rather selected group, the key predictors of the presence and progression of subclinical atherosclerosis were anything

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but surprising: older age, male sex, presence of diabetes and smoking. Collectively the prevalence and progression of CAC in this subgroup of individuals was mostly dependent on other well-known risk factors, not on the LDL-C levels. This would be expected considering the homogenously elevated LDL-C of the population.

Despite the limited sample size, presence and burden of CAC were clearly associated with both coronary heart disease and cardiovascular disease events during more than 13 years of follow-up. In light of the high prevalence of CAC = 0 in this population, a substantial proportion of individuals with significantly elevated LDL-C could be reclassified as lower risk in a follow-up extending more than 10 years. It is worth noting that in this group the absolute event rate was 3.7%, below the threshold of current ACC/AHA guidelines to recommend any pharmacologic treatment [3]. This is yet another piece of evidence substantiating the favorable prognostic value of CAC zero among those deemed high risk by traditional risk stratification strategies. These findings challenge current dogmatic conventions that risk in this population is so high that risk estimation is unjustified; in fact low risk individuals can be identified.

Although lifelong exposure to high LDL-C level is known to be associated with increased likelihood of subclinical and clinical atherosclerosis [10,11], this recent evidence [1] suggests this effect is heterogeneous, and a considerable subgroup of individuals with very high LDL-C does not develop coronary artery calcifications and has a very low event rate. It is important to highlight that in general those were older individuals followed for more than 13 years and population has reach ages above 75 years, though the sample size of the present study was relatively small, and the current evidence cannot be read as definitive.

The big question moving forward is how these findings with all the emerging data on the favorable prognosis on the power of zero inform practice? Both the current study and our previous report support [9] the consideration of CAC to guide treatment intensity of lipid lowering pharmacologic treatment even among those with significantly elevated LDL-C. From a practical standpoint, the unselected treatment of individuals with very high LDL-C (> 190mg/dL) irrespective of their clinical risk or the presence of subclinical atherosclerosis might not be the most prudent approach, though current evidence on how to best approach those individuals is still lacking. While non-pharmacologic interventions might be recommended to all, potentially statins could be offered with shared decision making to those with elevated LDL-C, though the benefit is less well documented in patients without subclinical atherosclerosis. More importantly, more expensive non-statin treatments should only be considered if there is evidence of extensive atherosclerotic disease based on CAC testing as may be the case in FH [12], though additional studies in those individuals are warranted.

From a more conceptual standpoint, the results of the two recent studies of individuals with very high LDL-C should make us question at least part of our understanding of the pathophysiology of the atherosclerotic process(1, 9). In particular, the identification of nearly 40% of individuals without atherosclerosis in these groups might be an adequate silo to investigate resilience to this disease despite known risk factors. It is unlikely that those individuals' endothelium survived without a scratch by chance. Is it the case that this population may allow us to better understand atherosclerosis, and maybe novel forms of treatment?

Declaration of competing interest

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