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Editorial

Baseline LDL-C levels and risk of cardiovascular events: is there any room for questions?

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Atherosclerotic cardiovascular disease (ASCVD) is a multifactorial condition and thus, results from a variable combination of several risk factors. According to a robust bulk of undeniable long-term evidence, LDL-cholesterol (LDL-C) represents one of the most important risk factors for ASCVD, particularly in the coronary bed. Indeed, not only observational studies, showing a direct association between cholesterol and cardiovascular events, but also genetic studies, and most importantly, intervention clinical trials with statins, ezetimibe and PCSK9 inhibitors, have all together proved the concept of LDL-C as a causal factor for ASCVD [1–4].

Elevated blood pressure is another important risk factor for ASCVD, with indisputable evidence showing an independent association between systolic blood pressure (SBP) and stroke, coronary events, heart failure and end-stage renal disease [5]. Many clinical intervention studies have strengthened the evidence on the association between blood pressure and ASCVD, given the significant risk reduction of cardiovascular and cerebrovascular outcomes with treatment of hypertension [6]. One of the seminal clinical trials in this field was SPRINT (Systolic Blood Pressure Intervention Trial). SPRINT was a randomized, open-label study of intensive *versus* standard blood-pressure control, conducted at several clinical sites in United States [5]. The trial, assigning 9361 individuals with SBP ≥ 130 mmHg and increased cardiovascular risk (but no diabetes), showed that a SBP goal of <120 mmHg (intensive treatment) resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, as compared to a goal of <140 mmHg (standard treatment).

In this issue of the journal Nguyen et al. reported a *post-hoc* analysis of the SPRINT trial that assessed the association of baseline LDL-C with cardiovascular outcomes in high-risk hypertensive patients. Surprisingly, results have showed that LDL-C was not associated with the primary outcome, a composite of various cardiovascular outcomes, all-cause mortality, and cardiovascular mortality, in the overall study cohort. In the group of patients with a previous history of cardiovascular disease ($n = 1562$), LDL-C was only marginally associated with the primary outcome. These results are intriguing, considering the clear association between blood cholesterol and cardiovascular outcomes, including vascular death, observed in previous large prospective observational studies. In the classic Multiple Risk Factor Intervention Trial (MRFIT) study, with over 350,000 men aged 35 to 57 years, the relationship between serum cholesterol and coronary heart disease death was continuous and graded [7]. In the Prospective Studies Collaboration, that included 61 prospective observational studies and almost 900,000 adults in primary prevention, lower total cholesterol was associated with lower ischemic heart disease mortality at all age ranges and at all blood pressure levels [8]. However, it is important to note that the proportional risk reduction associated with lower cholesterol levels in this meta-analysis decreased with increasing blood pressure [8] and SPRINT was a study conducted exclusively in hypertensive subjects, with over a third having baseline SBP ≥145 mmHg. Moreover, there are other baseline characteristics of SPRINT population that might have contributed to the lack of association between LDL-C and the cardiovascular outcomes in the study by Nguyen et al. In SPRINT, subjects were required to have an increased risk of cardiovascular events, and therefore there was a high proportion of individuals at old age (28% of individuals aged ≥75 y) [5]. Similarly to hypertension, age also attenuates the proportional relation between total cholesterol and ischemic heart disease mortality, despite greater absolute effects [8]. Furthermore, the association of total cholesterol with cerebrovascular events in those large observational studies also deserves particular attention. A weak positive association was observed only in middle age, and only in those with below-average blood pressure. At older ages and in particular for those with SBP ≥ 145 mmHg, total cholesterol was negatively associated with total stroke mortality. Therefore, it is important to recognize that the strength of association between cholesterol and vascular events, although positive in the overall population, is not uniform across subgroups, with a possibly attenuated effect among older and hypertensive individuals.

Additionally, in the study by Nguyen et al., the authors did not observe any threshold of LDL-C that was associated with a higher risk of cardiovascular events, even among subjects under use of statins

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($n = 4054$). However, one of the important limitations of this study consists in its *post-hoc* nature. Indeed, the main focus of SPRINT was the comparison of two anti-hypertensive treatment strategies, and thus, the possibility of residual confounding cannot be completely excluded from the analysis of LDL-C association with cardiovascular outcomes.

Although the study by Nguyen et al. raises a question about the relationship between LDL-C and events in hypertensive patients, it is never too much to recapitulate the large and solid evidence derived from statin intervention studies and other lipid-lowering trials, showing a significant and proportional association between LDL-C reduction and the reduction of cardiovascular events, including stroke [2–4,9]. Therefore, intensive LDL-C-lowering is recommended to high-risk individuals, particularly to secondary prevention patients, regardless of baseline levels, as also suggested by the authors. Interestingly though, in contrast to previous results, a recent meta-analysis observed that baseline LDL-C levels may influence the relative magnitude of lipid-lowering benefits. In this study, those subjects with higher baseline LDL-C levels derived greater cardiovascular benefit, particularly on mortality outcomes, from more intensive lipid-lowering therapies [10], supporting the prognostic relevance of baseline LDL-C levels.

In summary, in a *post-hoc* analysis, Nguyen et al. did not observe an association between LDL-C levels and cardiovascular outcomes in primary prevention patients from the SPRINT cohort, and found a marginal association among secondary prevention patients. Whether the presence of hypertension and the high prevalence of old-age individuals in the cohort have attenuated the power of this association, it remains to be determined. Importantly, LDL-C lowering still represents the mainstay of cardiovascular prevention, particularly the prevention of coronary events, in these high-risk patients.

Conflicts of interest declaration

VZR received honoraria for speaker activities from Amgen and Sanofi; RDS received honoraria for consulting, research and or speaker activities from Astra Zeneca, Amgen, Akcea, Biolab, Esperion, Kowa, Merck, MSD, Novo-Nordisk, and Sanofi/Regeneron.

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