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Cholesterol and inflammatory risk: Insights from secondary and primary prevention

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Low-density lipoprotein cholesterol (LDL-C) is undeniably causal for cardiovascular disease (CVD) [1]. Evidence from both the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial in patients with stable cardiovascular disease (CVD), and ODYSSEY Outcomes in acute coronary syndrome patients, supports a 'lower is better' strategy with no apparent lower threshold for benefit from LDL-C lowering. These data provide food for thought for guideline groups [2–4].

It is evident, however, that even at the very low LDL-C levels attained with PCSK9 inhibitors in these trials, patients continue to experience events, implying a role for other risk factors. Given that inflammation is integral to all stages of the atherosclerotic process, inflammatory mediators such as proinflammatory cytokines, are likely contenders. Indeed, with the results of CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), point to a role for anti-inflammatory therapies. Against a background of well controlled LDL-C levels at baseline (2.12 mmol/L vs. 2.38 mmol/L in FOURIER) patients with a previous myocardial infarction and elevated levels of C-reactive protein (≥2 mg/L) gained significant clinical benefit from treatment with canakinumab, a monoclonal antibody to interleukin-1β [5]. In subsequent analyses, modulation of the interleukin-6 signalling pathway by canakinumab was also shown to reduce cardiovascular events [6]. Once again, however, reducing inflammation with canakinumab did not eliminate the risk of cardiovascular events in these high-risk patients.

But is inflammatory risk still relevant when LDL-C levels are very low? Analyses from both FOURIER and the SPIRE Outcomes trials (SPIRE 1 and SPIRE 2 with bococizumab) have been instructive. In FOURIER, patients were categorized by baseline CRP level (< 1 mg/L, 1–3 mg/L, and > 3 mg/L) [7]. Not surprisingly, as CRP is a marker of absolute risk, patients with the highest CRP levels at baseline had the highest incidence of cardiovascular events (ranging from 12% to 13.7%–18.1%, respectively, for the primary outcome, a 5-point composite of major adverse cardiovascular events). Both LDL-C and CRP were shown to be independently associated with clinical outcome. Therefore, even at LDL-C levels of 0.52 mmol/L (20 mg/dL) on evolocumab treatment, higher CRP levels at baseline increased cardiovascular risk over the trial. Similar findings were reported for the SPIRE Outcome trials, where higher CRP levels at baseline increased the risk of major adverse cardiovascular events, even after adjustment for on-treatment LDL-C levels [8].

In the era of highly efficacious LDL-lowering therapy, do these results also apply to the real-world high-risk primary prevention setting? Findings from the REGARDS (Reasons for Geographical and Racial Differences in Stroke) study provide insights [9]. The REGARDS cohort is a population of more than 30,000 individuals (non-Hispanic black or white individuals, aged at least 45 years) recruited from within communities in the USA between 2003 and 2007, who were subsequently followed by telephone interview at 6-monthly intervals to detect suspected cardiovascular events. The current analysis relates to a subgroup of primary prevention individuals with high baseline risk, as defined by 10-year Framingham risk ≥10% for coronary heart disease (CHD) or ≥7.5% for atherosclerotic CVD. Patients were categorized by baseline LDL-C (< 1.8 mmol/L [70 mg/dL] or ≥ 1.8 mmol/L) and by CRP levels (< 2 and ≥ 2 mg/L). The outcomes of interest were all-cause mortality, incident CHD, and incident stroke.

Overall, data from 6136 high-risk primary prevention individuals (mean age 67.6 years, 67% men, 42% black) were included, of whom 308 (5%) had a baseline LDL-C level < 1.8 mmol/L (70 mg/dL). Over the follow-up period (ranging from a mean of 6.91 years for coronary events, 7.14 for all-cause death, to 8.63 years for stroke), 1376 (22.4%) individuals had a fatal event, 508 (8.3%) had a coronary event, and 352

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(5.7%) had a stroke.

The results pose a couple of conundrums. First, there was evidence of a significant non-linear relationship between LDL-C level and all-cause death; LDL-C levels between 1.8 mmol/L (70 mg/dL) and 5.2 mmol/L (200 mg/dL) were protective but there was no further benefit at lower LDL-C levels. There was also no statistically significant relationship between the LDL-C level and CHD. These findings would appear to directly oppose extensive evidence for the 'lower is better' strategy for LDL-C, supported by both the FOURIER and ODYSSEY Outcome studies· [2,3,10] However, a number of reasons may explain these differences. First, the REGARDS analysis related to a primary prevention population, and it is likely that there are physiological differences compared with secondary prevention clinical trial cohorts. Second, in REGARDS LDL-C was only reported at baseline and not throughout the follow-up period as in clinical trials and therefore confounding due to subsequent initiation (or discontinuation) of LDL-C lowering therapy during follow-up in individuals with high LDL-C levels at baseline cannot be discounted. Third, given the small sample size (5%) with baseline LDL-C < 1.8 mmol/L, the possibility of bias cannot be excluded. Finally, as for all observational studies, the REGARDS study is likely to be confounded and cannot detract from results of the LDL lowering benefit shown in randomized clinical trials at much lower LDL-C levels.

A second key finding was that concomitant low LDL-C (< 1.8 mmol/L) did not decrease the risk associated with high CRP levels (≥ 2 mg/L). This reinforces the importance of inflammatory risk as reported in CANTOS, even in a primary prevention population. The question remains which stimuli trigger inflammation: LDL remains the most credible candidate.

Implications

So, what is the overall take home message from these reports? As a general rule, it is important to bear in mind that a primary prevention real-world population is likely to be more heterogeneous than secondary prevention cohorts in clinical trials, and therefore it is not possible to compare these groups directly. Despite this caveat, however, it is clear that cholesterol risk and inflammatory risk are relevant to both settings; moreover, the REGARDS study shows the importance of high inflammatory risk even with inherently low LDL-C levels at baseline in the primary prevention setting.

Conflicts of interest

The author declared she do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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