Circulation

EDITORIAL

Low-Grade Inflammation Modifies Cardiovascular Risk Even at Very Low LDL-C Levels

Are We Aiming for a Dual Target Concept?

Articles, see p 131 and p 141

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Patients after myocardial infarction (MI) are at increased risk for a recurrent event despite widespread early revascularization and established polypharmacotherapy.

Various long-term studies like GRACE (Global Registry of Acute Coronary Events)[1] and the large Swedish national registries[2] have shown that, 5 years after the index event, >20% of patients have experienced recurrent MI, stroke, or cardiovascular death. In addition, a recent registry[3] from the Netherlands has shown that >20% of patients had a >30% risk for recurrent vascular events over 10 years, in particular, those with polyvascular disease that largely persisted even after estimating the effects of a potential reduction through aggressive therapy of various established risk factors. Thus, there is unequivocal evidence of a considerable residual risk in patients post-MI that, to a significant extent, may not only be attributable to suboptimal treatment of elevated low-density lipoprotein cholesterol (LDL-C) levels and other risk factors, but also leaves room for further pathophysiological mechanisms like a prolonged inflammatory response.

SUBCLINICAL INFLAMMATION IS ASSOCIATED WITH INCREASED CARDIOVASCULAR RISK

In large-scale observational studies, either in apparently healthy subjects[4] or in patients with manifest atherosclerosis as in the STABILITY trial (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy),[5] elevated levels of various proinflammatory molecules such as cytokines and acute-phase reactants have been associated not only with adverse cardiovascular outcomes, but also with noncardiovascular outcomes. In addition, recent data by Dutta et al[6] have clearly shown that an acute MI accelerates the atherosclerotic process by activation of the sympathetic nerve system followed by an increased progenitor release from the bone marrow niche. This subsequently promotes extramedullary monocytopoiesis, thus potentially fostering repeat plaque rupture. Hence, inflammation has been clearly shown to be involved in all stages of the atherosclerotic process from endothelial dysfunction through plaque formation and finally to erosion or plaque rupture that may ultimately lead to an ischemic syndrome.

RESIDUAL CHOLESTEROL RISK VERSUS RESIDUAL INFLAMMATORY RISK

The introduction of PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitors has opened new options for patients at high risk to achieve unprecedented

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low LDL-C levels for further residual risk reduction. Meanwhile, 3 large clinical end point studies, FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk),[7] SPIRE (Studies of PCSK9 Inhibition and Reduction of Vascular Events),[8] and, most recently, ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab),[9] have consistently shown a 15% to 20% relative risk reduction for major cardiovascular end points. For example, in FOURIER there was a reduction of the key secondary 3-point major adverse cardiovascular event end point (myocardial infarction, stroke, and cardiovascular death) from 9.9% to 7.9% over 36 months, corresponding to an absolute risk reduction of 2%, yet still leaving a significant number of patients even on extremely low LDL-C levels of ≈30 mg/dL with a substantial residual risk. However, the recent CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)[10] has ultimately proven that inflammation can no longer be considered a bystander in atherogenesis but rather represents an important target for intervention. In CANTOS, the primary 3-point major adverse cardiovascular event end point in the total study population could also be reduced by 15%, yet by 27% in those who showed a robust response with a significant decrease of high-sensitivity C-reactive protein (hsCRP), albeit also leaving a substantial number of patients at further increased risk. Thus, one might assume at least 2 scenarios: one with residual cholesterol risk after MI if LDL-C goals have not been reached but without significant subclinical systemic inflammation, and, on the other hand, residual inflammatory risk in the presence of achieved LDL-C targets.

Based on data from the FOURIER and SPIRE trials, 2 articles in this issue of *Circulation*[11,12] have addressed the interesting question whether or not inflammation may still be an important issue even after very low LDL-C levels have been achieved. All 3 aforementioned PCSK9 inhibitor studies have shown that inhibition of PCSK9 does not affect systemic inflammation, and, vice versa, treatment with canakinumab, the anti–interleukin-1β antibody used in CANTOS, does not modify LDL-C levels.

Thus, in FOURIER, patients were categorized according to their baseline hsCRP level into those <1 mg/L, between 1 and 3 mg/L, and >3 mg/L with a median level of 1.8 mg/L.

Because hsCRP clearly represents an established marker of risk, as expected in the placebo group, higher baseline hsCRP categories were associated with worse outcome, and across hsCRP categories there was an increase from 12% to 13.7% to 18.1% of events for the primary end point and from 7.4% to 9.1% and 13.2% for the key secondary end point. Relative risk reductions for both end points were consistent across hsCRP strata. However, absolute risk reductions with evolocumab were greater in those with higher hsCRP. Further analysis showed that both LDL-C and hsCRP were independently associated with the primary outcome. Similar to what has been shown post hoc in 10 major statin trials[13,14] and prospectively in the JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin),[15] the greatest benefit was achieved in those with the lowest LDL-C levels and the lowest hsCRP concentrations. Thus, in FOURIER patients with achieved LDL-C concentrations as low as <20 mg/dL taken after 1 month of evolocumab therapy, hsCRP was able to modify the relationship with various 3-year event rates, suggesting that, even at such extremely low levels of LDL-C, inflammatory processes still play a role.

The second article used the SPIRE Outcomes Trial to assess the same question. Out of >27 000 patients in SPIRE 1 and SPIRE 2, 9732 patients received both statin therapy and bococizumab, a humanized monoclonal antibody against PCSK9. These patients were evaluated according to their on-treatment levels of hsCRP and LDL-C measured 14 weeks after drug initiation, and a primary end point consisting of nonfatal MI, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death was used. LDL-C reduction at 14 weeks was similar to what had been observed in FOURIER and in ODYSSEY, ≈60%, whereas hsCRP levels did not change, as expected. Again, in agreement with observations in FOURIER, in SPIRE 1 and 2 increasing on-treatment hsCRP concentrations were not only associated with an increased risk for the primary end point, but also for the individual end points MI, cardiovascular death, and total mortality, and these relationships were even present after adjustment for traditional risk factors and LDL-C on treatment. Furthermore, relative risk reductions with bococizumab were similar across hsCRP on-treatment levels. Thus, consequently, the authors came up with the same conclusion, namely residual inflammatory risk persists at even low LDL-C levels in patients treated both with a statin and a PCSK9 inhibitor.

What can we learn from these post hoc analyses in 2 large, well-conducted clinical trials with 2 different PCSK9 inhibitors in patients at high risk already on statin treatment? First, hsCRP remains a risk marker across all categories of achieved LDL-C levels. Second, the relative risk reduction by a PCSK9 inhibitor in various hsCRP categories was similar, yet, based on the different risk carried about by increasing hsCRP concentrations, the absolute risk reduction in higher hsCRP categories was larger. All 3 PCSK9 inhibitor trials, and the anti-inflammatory CANTOS trial, as well, were still associated with

a considerable residual risk, despite proving the effectiveness of the respective therapies. Thus, one might conclude that there is no dichotomous situation of a residual cholesterol versus a residual inflammatory risk, but rather these data support a combination strategy to treat both, LDL-C, and the anti-inflammatory response, as well, as aggressively as possible to further reduce residual risk.

LIMITATIONS AND STRENGTHS OF THE PRESENTED ANALYSES

These 2 analyses from the FOURIER and SPIRE trials have some limitations. First, both represent post hoc analyses, and thus residual confounding remains an issue. Second, on-treatment LDL-C concentrations were not randomized; and third, in the SPIRE program, hsCRP was not available in a significant number of study participants. However, the results of both studies are consistent and have been derived from large clinical trials.

PERSPECTIVES

On the basis of what we have learned about inflammation and atherosclerotic complications from basic science and clinical studies, determining future cardiovascular risk at even very low levels of LDL-C, should we indeed pave the way for a combination therapy? Pushing things forward from a vigorous scientific standpoint, one might only be able to answer this question by performing a prospective 2×2 factorial trial with aggressive lipid-lowering and anti-inflammatory treatment. However, the possibility that this will be done by using 2 monoclonal antibodies is fairly unrealistic. Yet, there are other anti-inflammatory and also lipid-lowering drugs on the horizon that could play a role in the future to finally answer this question. For the time being, these post hoc analyses from FOURIER and the SPIRE program provide consistent evidence for the presence of a prolonged inflammatory response in patients at high risk for recurrent cardiovascular events despite having achieved very low LDL-C levels.

ARTICLE INFORMATION

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