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HOW TO ADDRESS RESIDUAL RISK POST-ACS: LDL-C, DYSLIPIDEMIA, AND INFLAMMATION

Despite optimal treatment for secondary prevention after an acute coronary syndrome (ACS), there is still a considerable residual risk burden. Beyond persisting high levels of cholesterol, inflammation and high triglyceride levels can contribute to this burden. It is therefore critical to not only develop medicines that can further lower LDL-c levels, but also to target the disease process in a multifactorial fashion. This can, for example, be achieved by targeting inflammatory pathways. During the ESC in Rome this year, the Physicians' Academy for Cardiovascular Education (PACE) organised a satellite symposium in which residual risk targeting was discussed, including LDL-c-lowering approaches beyond statins and alternative approaches to target residual risk.

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Inflammation as potential target for therapy to target residual risk post ACS

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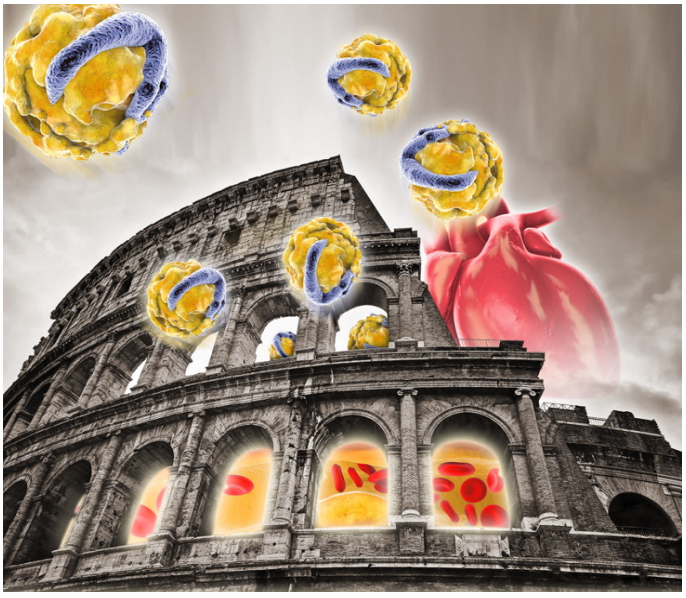
After treatment with high-intensity statins, patients can still have residual cholesterol risk or residual inflammatory risk. This means that patients still have either high levels of LDL-c, but normal high sensitivity C-reactive protein (hsCRP) or normal LDL-c but high hsCRP. Both patient groups need additional care to reduce LDL-c levels or inflammatory burden.
Ridker recently reported on the impact of residual inflammation. He showed a continuous positive linear association between hsCRP levels and relative risk of future events. The question now is, whether lowering these levels would also result in a lower CV risk. This seems plausible, as it has been demonstrated that the magnitude of independent risk associated with inflammation is at least as large, if not larger, than that of blood pressure and cholesterol. Furthermore, lowering LDL-c as well as hsCRP using statin monotherapy or statins plus ezetimibe in the PROVE-IT and IMPROVE-IT studies, significantly improved the frequency of recurrent vascular events[1,2].

"The magnitude of independent risk associated with inflammation is at least as large, if not larger, than that of blood pressure and cholesterol."

These data support the idea of additional CV benefit when inhibiting inflammatory pathways specifically, for example by targeting IL-1 and IL-6 pathways. Main downstream targets of these pathways are fibrinogen and CRP and indeed, individuals with low CRP levels due to polymorphisms in genes involved in the IL-6 pathway, have a lower risk of coronary heart disease[3,4].



Two on-going trials currently investigate whether specific reduction of inflammation reduces CV event rates. One of these trials is the 'cardiovascular inflammation reduction trial' (CIRT), in which low doses of methotrexate are used. The idea of using methotrexate (MTX) is distilled from an observation in rheumatoid arthritis patients. MTX-treated patients have reduced CV event rates[5]. Moreover, cholesterol-fed rabbits that were given MTX showed less evidence of cholesterol plaque in the arteries compared to control rabbits. In the CIRT trial, 7000 patients on statins, ACE/ARBs, BB, ASA are being enrolled that have evidence of inflammation, diabetes or metabolic syndrome. Patients are randomised to 15-52 mg MTX once a week or placebo, for 3 years and will be evaluated for non-fatal myocardial infarction (MI), non-fatal stroke or CV death.
The other trial is the event-rate driven 'canakinumab anti-inflammatory thrombosis outcomes study' (CANTOS), which is now fully enrolled (10.064 patients) and will be read out within the next 12 months. Patients on statins, ACE/ARBs, BB, ASA and with persistent elevation of hsCRP were given a monoclonal IL-1ß antibody, canakinumab, which neutralises the bioactivity of this pro-inflammatory cytokine. The phase II study of this antibody already demonstrated that IL-6, hsCRP and fibrinogen were lowered when canakinumab was administered every 3 months[6]. CANTOS investigates whether the non-fatal MI, non-fatal stroke and CV event rate will be reduced in patients randomised to 50, 150 or 300 mg canakinumab every 3 months or placebo.
Other on-going studies with regard to anti-inflammatory regimes include the LODOKO trial in which colchicine reduced secondary CV disease. This regime is now being repeated by multiple groups around the world. Unfortunately, not all anti-inflammatory drugs give the desired effect; the losmapimod MAP-kinase inhibitor did not result in reduced cardiovascular CV outcomes in patients with prior acute MI[7].
More work needs to be done to increase survival of ACS patients. In this respect, Ridker emphasised that in addition to the residual cholesterol and inflammatory risk, residual triglyceride risk is another interesting area of research that can take this issue forward and should be elaborated on.

Beyond statins: The role of ezetimibe in targeting residual

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ACS patients who are not at LDL-c treatment goal despite statin therapy, currently have two options; increasing statin dose or receiving combination therapy. More cholesterol-lowering drugs are available beyond statins, including ezetimibe, which can be used in combinational setting to further reduce residual CV risk. Statins and ezetimibe both affect the bulk metabolism of cholesterol in the body. While statins reduce cholesterol synthesis in the liver, ezetimibe blocks cholesterol absorption in the gut and thereby enhances the excretion of cholesterol. Combining these drugs introduces a double cholesterol-affecting hit and is therefore attractive to use.

"The double hit affects cholesterol metabolism in the whole body and is attractive in terms of the complementarity of action"

The benefit of this combination therapy is evidenced by the IMPROVE-IT study, which revealed an extra reduction of approximately 20% when using ezetimibe on top of statins. This study also showed a subsequent 6-8% reduction of CV disease, MI and stroke endpoints[2]. A Mendelian randomisation trial confirmed the conclusions of the IMPROVE-IT study, as the combination of a reduced gastrointestinal absorption and suppressed synthesis of LDL-c due to genetic variants in HMGR and NPC1L1, also lowered coronary heart disease risk[8].
The IMPROVE-IT trial further demonstrated that ezetimibe did not only affect the frequency of first events but also of a secondary, third and fourth event. Such a trend had also been observed with statins, which Packard illustrated with data from the WOSCOPS trial. In the WOSCOPS trial pravastatin treatment for only 5 years resulted in a benefit that persisted for at least 20 years[9]. Another conclusion deduced from the IMPROVE-IT trial was that also this trial fitted with the observation that every 1 mmol/L reduction of LDL-c translates into a 22% decrease of risk. This insight corroborates the concept of further LDL-c lowering beyond statins in different clinical situations.
Packard also underlined the possibility of statin dose-lowering when using ezetimibe. This enables minimisation of statin-related adverse events that individuals can experience and may be worried about, while still maximising the benefit.

Novel strategies targeting residual risk: The promise of PCSK9 inhibiting therapies

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Stroes further elaborated on achieving additional LDL-c reduction beyond statins, focussing on PCSK9 inhibitors. He further underscored the significance of LDL-c-lowering, as illustrated by the beneficial relation between genetically and therapeutically lower LDL-c and coronary

heart disease (CHD) risk and between statin-achieved LDL-c levels and cardiovascular CV risk. These beneficial relationships have also been observed in individual trials such as TNT, JUPITER and PROVE-IT1,[10-11].

Using statins, only 20% of hypercholesterolaemic patients achieve an LDL-c level <70 mg/dL as specified by guidelines and a similar proportion of FH patients reach their LDL-c target. Moreover, adverse effects like muscle symptoms appear to be a major cause for therapy discontinuation and thereby reduce survival changes. Therefore, additional LDL-c-lowering therapy is needed in high-risk patients, special patient populations in which the LDL-c goal is not achieved with statins, such as FH patients, or in patients with adverse effects on statins.

Like ezetimibe, PCSK9 inhibitors can further lower LDL-c levels. Under normal circumstances, PCSK9 can bind the LDL receptor (LDLR), whereupon it is degraded in the liver. PCSK9 antibodies interfere with this process, resulting in enhanced levels of LDLR proteins on the cell surface that can catch LDL particles from the circulation and thereby target LDL for degradation. It has been shown by genetic studies that loss of function of PCSK9 results in low LDL-c levels and low CHD risk. Furthermore, an additive effect of having both a PCSK9 SNP and HMGR SNP[12], a protein that is involved in the LDL-c metabolism targeted by statins, is suggested. This suggests that additional PCSK9 inhibition will benefit patients at high CV risk.

CV benefit gained by PCSK9 inhibition has already been shown with the PCSK9 inhibitor evolocumab that induced a rapid LDL-c decrease of approximately 50-60%. This reduction was persistent for at least 52 weeks[13-14]. Furthermore, the magnitude of this PCSK9-inhibiting effect was independent of baseline characteristics[15]. In statin-intolerant patients, LDL-c reduction was similar, and evolocumab was well tolerated[14]. The safety of PCSK9 inhibitors can only be evaluated in about 5 to 10 years, but up to now there do not seem to be any major adverse effects. Moreover, efficacy data of the OSLER study showed a trend towards reduced CV disease using evolocumab[14]. Another PCSK9 inhibitor, alirocumab, showed similar results[16].

Inflammatory instable lesions importantly contribute to the increased risk of recurrent events in the first year after ACS. It is still questionable whether PCSK9 inhibitors have similar anti-inflammatory effect similar to statins. Although CRP levels do not seem to change after PCSK9-inhibiting treatment, very preliminary data of Stroes do not rule out a protective effect of PCSK9 inhibitors through anti-inflammatory mechanisms. To further corroborate this possible protective effect, Stroes went back to the causal effect of atherosclerosis, which is dictated by macrophages. It was recently shown that next to hsCRP, accumulation of white blood cells, such as macrophages, in the atherosclerotic plaque may predict the overall inflammatory state of the aortic atherosclerotic wall.

Preliminary data now seem to indicate that a reduction in LDL-c through PCSK9 inhibition or other mechanisms, decrease the increased mobility of specific white blood cells towards the plaque, which had been activated when cholesterol levels increased. These data may therefore suggest that PCSK9 inhibitors, or any other mechanism that reduces LDL-c, might affect inflammation through alleviating activation of specific white blood cells.

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