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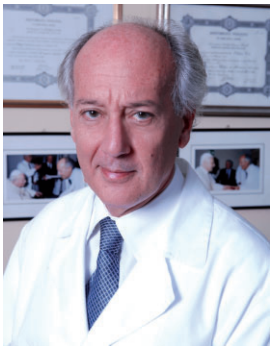
An update on triglyceride-rich lipoproteins and their remnants in atherosclerotic cardiovascular disease



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Residual cardiovascular risk in patients on optimized LDL-lowering therapy remains a hot topic. While inflammation explains part of the residual risk,[1–3] triglyceride-rich lipoproteins and their remnants also may play an important role.[4–6] This Focus Issue on dyslipidaemias contains the Special Article entitled '**Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society**' by Henry Ginsberg from Columbia University in New York, NY, USA.[7] The authors point out that recent advances in human genetics, together with a large body of epidemiological, pre-clinical, and clinical trial results, provide strong support for a causal association between triglycerides (TG), TG-rich lipoproteins (TRLs), and TRL remnants, and increased risk of myocardial infarction (MI), ischaemic stroke, and aortic valve stenosis. This consensus statement critically appraises current understanding of the structure, function, and metabolism of TRLs, and their pathophysiological role in atherosclerotic cardiovascular disease (ASCVD). Key points are: (i) a working definition of normo- and hypertriglyceridaemic states and their relationship to risk of ASCVD; (ii) a conceptual framework for the generation of remnants due to dysregulation of TRL production, lipolysis, and remodelling, as well as clearance of remnant lipoproteins from the circulation; (iii) the pleiotropic proatherogenic actions of TRLs and remnants at the arterial wall; (iv) challenges in defining, quantifying, and assessing the atherogenic properties of remnant particles; and (v) exploration of the relative atherogenicity of TRLs and remnants compared with LDL. Assessment of these issues provides a foundation for evaluating approaches to effectively reduce levels of TRLs and remnants by targeting either production, lipolysis, or hepatic clearance, or a combination of these mechanisms. This consensus statement updates current understanding in an integrated manner, thereby providing a platform for new therapeutic paradigms targeting TRLs and their remnants, with the aim of reducing the risk of ASCVD.

The role of omega-3 fatty acids in the prevention of cardiovascular risk remains controversial.[8] In a Fast Track article entitled '**A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs**', Takahito Doi from the Copenhagen University Hospital in Denmark, and colleagues tested the hypothesis that the contrasting results for the effect of high-dose, purified omega-3 fatty acids on the prevention of ASCVD in two randomized trials, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) vs. Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridaemia (STRENGTH), can be explained by differences in the effect of active and comparator oils on lipid traits and C-reactive protein.[9] In the Copenhagen General Population Study (CGPS) with 106 088 individuals, to mimic trial designs, the authors analysed those who met key inclusion criteria in REDUCE-IT (n = 5684; ASCVD = 852) and STRENGTH (n = 6862; ASCVD = 697). The incidence of ASCVD was followed for the median durations of REDUCE-IT and STRENGTH (4.9 and 3.5 years, respectively). When combining changes in plasma triglycerides, LDL cholesterol, and C-reactive protein observed in the active oil groups of the original studies, estimated hazard ratios (HRs) for ASCVD in the CGPS were 0.96 [95% confidence interval (CI) 0.93–0.99] mimicking REDUCE-IT, and 0.94 (95% CI 0.91–0.98) mimicking STRENGTH. In the comparator oil groups, corresponding HRs were 1.07 (95% CI 1.04–1.10) and 0.99 (95% CI 0.98–0.99). Combining these results, the active oil vs. comparator oil HR was 0.88 (95% CI 0.84–0.93) in the CGPS mimicking REDUCE-

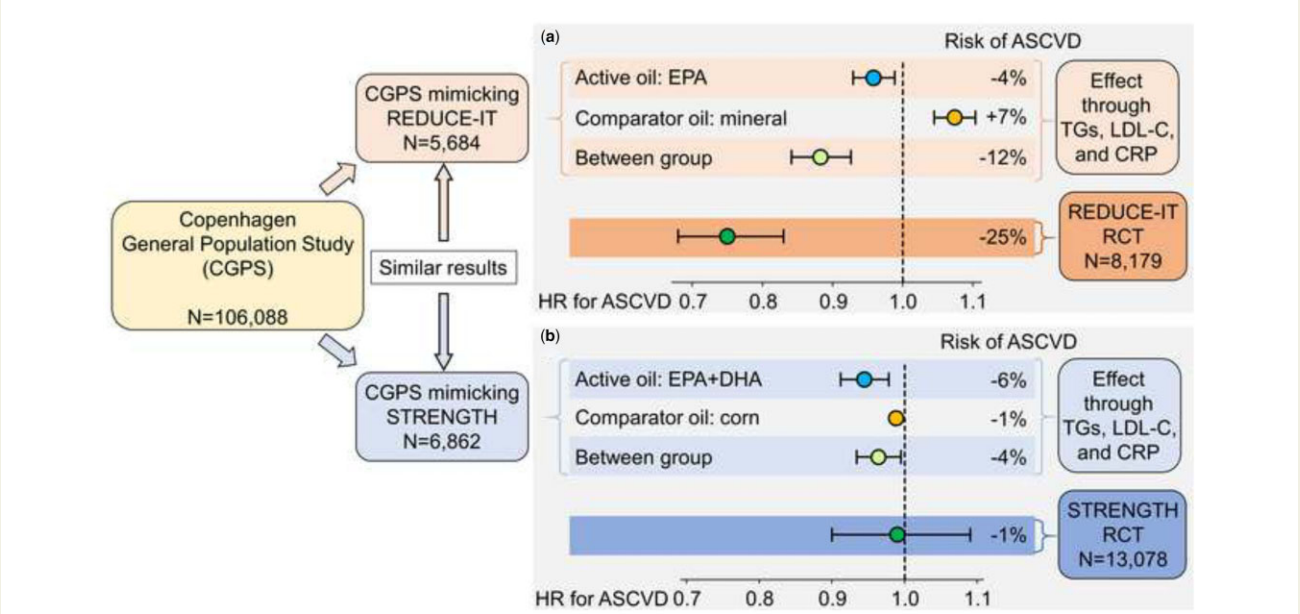

Figure 1 Graphical Abstract (from Doi T, Langsted A, Nordestgaard BG. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs. See pages 4807–4817).

IT, compared with 0.75 (95% CI 0.68–0.83) in the REDUCE-IT. The corresponding HR was 0.96 (95% CI 0.93–0.99) in the CGPS mimicking STRENGTH, compared with 0.99 (95% CI 0.90–1.09) in STRENGTH (*Figure 1*).

The authors conclude that the contrasting results of REDUCE-IT vs. STRENGTH can partly be explained by a difference in the effect of comparator oils (mineral vs. corn), but not of active oils [eicosapentaenoic acid (EPA) vs. EPA + docosahexaenoic acid], on lipid traits and C-reactive protein. The contribution is accompanied by an **Editorial** by Kevin Maki from the School of Public Health Bloomington in Indiana, USA.[10] In conclusion, Maki points out that current European guidelines recommend consideration of icosapent ethyl in combination with statin therapy for high- and very-high-risk patients with triglyceride concentrations in the range of 135–499 mg/dL (1.5–5.6 mmol/L) despite statin treatment for reduction of ASCVD risk, although important questions remain. Additional randomized, controlled trials of ASCVD outcomes and surrogate indicators, such as coronary plaque progression, will be needed to further clarify the magnitude of the effect of icosapent ethyl on ASCVD incidence, and the mechanisms responsible for such benefits.

Acute arterial vascular events in the coronary, cerebrovascular, and peripheral beds are often critical or disabling, and represent the most feared manifestations of atherosclerosis. While these acute events across vascular territories share related underlying pathobiologies, the total burden of acute arterial events has rarely been described in an at-risk cohort; nor has the aggregate impact of lipid-lowering therapy on pan-vascular acute events been well described. In another Fast Track article entitled '**Effect of evolocumab on acute arterial events across all vascular territories: results from the FOURIER trial**', Kazuma Oyama from the Harvard Medical School in Boston, MA, USA, and colleagues assessed the impact of the proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor evolocumab on acute arterial events across all vascular territories, including coronary, cerebrovascular, and peripheral vascular beds, in patients with established ASCVD.[11] In the FOURIER trial, 27 564 patients with stable ASCVD on statin therapy were randomly assigned to evolocumab or placebo. Acute arterial events were a composite of acute coronary (coronary heart disease death, MI, or urgent coronary revascularization), cerebrovascular (ischaemic stroke, transient ischaemic attack, or urgent cerebral revascularization), or peripheral vascular (acute limb ischaemia, major amputation, or urgent peripheral revascularization) events. Of the 2210 first acute arterial events, 74% were coronary, 22% were cerebrovascular, and 4% were peripheral vascular. Evolocumab reduced first acute arterial events by 19% (HR 0.81; $P < 0.001$), with significant individual reductions in acute coronary (HR 0.83), cerebrovascular (HR 0.77), and peripheral vascular (HR 0.58) events. There were 3437 total events (first plus recurrent), with evolocumab reducing total events by 24% (incidence rate ratio 0.76). The magnitude of reduction in acute arterial events with evolocumab numerically increased over time, with a significant 16% reduction (HR 0.84) in the first year followed by a 24% reduction (HR 0.76) thereafter (*Figure 2*).

Oyama *et al.* conclude that the addition of the PCSK9 inhibitor evolocumab to statin therapy reduces acute arterial events across all vascular territories with a robust effect over time, indicating a pan-vascular impact of aggressive lipid-lowering therapy on these acute and clinically meaningful events. The manuscript is accompanied by a thought-provoking **Editorial** by Carl Orringer from the University of Miami Miller School of Medicine in Florida, USA.[12] Orringer notes that an expanded role for PCSK9 inhibitors to treat acute arterial events is of great clinical interest. Yet, the apparently greater reported effect of evolocumab therapy on acute

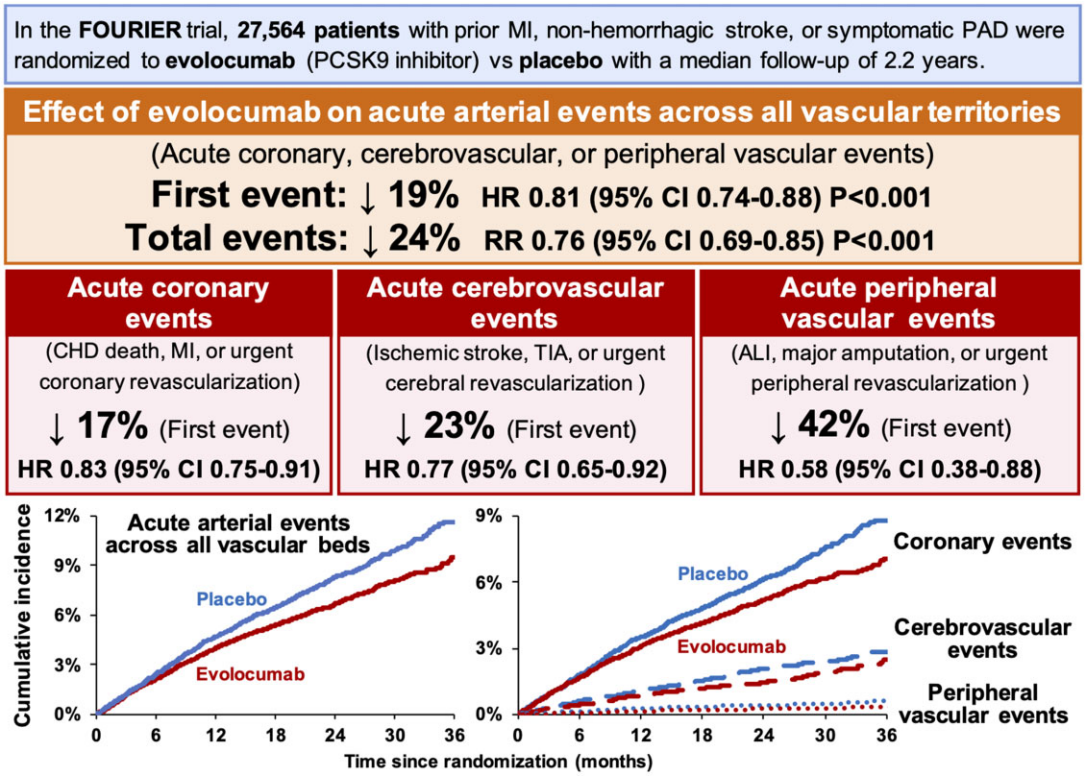

Figure 2 Graphical Abstract (Oyama K, Giugliano RP, Tang M, Bonaca MP, Saver JL, Murphy SA, Ruzza A, Keech AC, Sever PS, Sabatine MS, Bergmark BA. Effect of evolocumab on acute arterial events across all vascular territories: results from the FOURIER trial. See pages 4821–4829).

cerebrovascular or peripheral vascular events observed by Oyama may be related to the smaller number of events in those vascular distributions as compared with coronary events. The results of future randomized controlled trials will provide a more definitive answer about whether such therapy provides a therapeutically beneficial and cost-effective approach to preventive therapy in this very high risk population.

In a Clinical Research article entitled '**Directly measured vs. calculated remnant cholesterol identifies additional overlooked individuals in the general population at higher risk of myocardial infarction**', Anette Varbo and Børge Nordestgaard from the Copenhagen University Hospital in Denmark tested the hypothesis that high directly measured remnant cholesterol is associated with increased risk of IHD and MI in the general population.[13] The authors also explored whether directly measured vs. calculated remnant cholesterol is superior in identifying individuals at increased risk. Overall, 16 207 individuals with both directly measured and calculated remnant cholesterol were followed up for 14 years to analyse the risk for IHD and MI. Compared with individuals with both directly measured and calculated remnant cholesterol <80th percentile (75% of the whole population), those with only directly measured remnant cholesterol ≥80th percentile had a HR of 1.42 for IHD and of 1.83 for MI. Corresponding HRs for individuals with only calculated remnant cholesterol ≥80th percentile (5%) were 1.14 and 1.14, respectively, and corresponding HRs for individuals with both directly measured and calculated remnant cholesterol ≥80th percentiles (15%) were 1.48 and 1.67, respectively.

The authors conclude that directly measured vs. calculated remnant cholesterol identifies 5% of overlooked individuals in the general population with cholesterol-rich, TG-poor remnants and 1.8-fold increased risk of MI. This manuscript is accompanied by an interesting **Editorial** by Alberico Luigi Catapano and Angela Pirillo from the University of Milan in Italy.[14] The authors conclude that the need for a clear definition of remnants has raised its head. Further research is warranted to obtain a recognized clinical method for accurate measurement of remnant cholesterol levels, which should include an in-depth characterization of measured lipoproteins and the validation in other populations. This will allow the comparison between studies and the validation of remnant cholesterol as a potential target for therapy.

Atherosclerosis is a chronic progressive inflammatory disease involving the synergistic interaction of lipid metabolic factors with the cellular components of the vessels. Formation of macrophage-derived foam cells is the hallmark of atherosclerosis.[15–17] During atherogenesis, monocytes are differentiated into macrophages in the subendothelial space and internalize oxidized LDLs (oxLDLs) through scavenger receptors such as SR-A and CD36. The interplay between the scavenger receptors and oxLDLs in macrophages induces the secretion of cytokines that recruit immune cells into the vascular wall. Increased uptake of oxLDLs and/or reduced cholesterol

efflux leads to lipid dysregulation in macrophages and promotes foam cell formation, triggering a series of inflammatory responses, ultimately establishing plaque formation and atherosclerotic lesions. This issue contains the Translational Research article entitled '**Macrophage NFATc3 prevents foam cell formation and atherosclerosis: evidence and mechanisms**', by Xiu Liu from the Zhongshan School of Medicine in Guangzhou, China, and colleagues.[18] This study investigated the specific role of macrophage calcineurin–nuclear factor of activated T-cell (NFAT)c3 in atherogenesis. Macrophage-specific NFATc3 knockout mice were generated in a mouse model of adeno-associated virus-mutant PCSK9-induced atherosclerosis. NFATc3 deficiency in macrophages promoted foam cell formation by potentiating SR-A- and CD36-mediated lipid uptake. NFATc3 directly targeted and transcriptionally up-regulated miR-204 levels. Mature miR-204-5p suppressed SR-A expression via canonical regulation. Restoration of miR-204 abolished the proatherogenic phenotype observed in the macrophage-specific NFATc3 knockout mice, and blockade of miR-204 function reversed the beneficial effects of NFATc3 in macrophages.

The authors conclude that macrophage NFATc3 up-regulates miR-204 to reduce SR-A and CD36 levels, thereby preventing foam cell formation and atherosclerosis, indicating that the NFATc3/miR-204 axis may be a potential therapeutic target against atherosclerosis. The contribution is accompanied by an **Editorial** by Kathryn Moore and Coen van Solingen from the New York University School of Medicine in New York, USA.[19] They highlight that the identification of the NFATc3-regulated nuclear miR-204-3p/CD36 and cytoplasmic miR-204-5p/SR-A axes adds new layers to our understanding of the regulation of foam cell formation and atherogenesis. The ability of NFATc3 to coordinately inhibit the expression of two important scavenger receptors for foam cell formation, and its down-regulation in monocytes and plaque macrophages of patients with CVD, identify NFATc3 as a potential therapeutic target for the treatment of atherosclerosis.

The issue is also complemented by two Discussion Forum contributions. In a commentary entitled '**The reduction in cardiovascular risk in REDUCE-IT is due to eicosapentaenoic acid in icosapent ethyl**',[20] Philippe Gabriel Steg from the Université de Paris in France, and Deepak Bhatt from Harvard Medical School comment on the recent publication '**A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs**' by Takahito Doi from the Copenhagen University in Denmark.[9,20] Doi *et al*. respond in a separate comment.[21]

The editors hope that this issue of the *European Heart Journal* will be of interest to its readers.

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