From prevention to plaque rupture and infarction

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Statins are a cornerstone of cardiovascular prevention and are highly recommended in current guidelines. However, statin-associated muscle symptoms are one of the principal reasons for statin non-adherence and/or discontinuation, contributing to adverse cardiovascular outcomes.

The issue contains a timely Consensus Paper by Erik S.G. Stroes from the Academic Medical Center in Amsterdam, The Netherlands entitled 'Statin-associated muscle symptoms: impact on statin therapy. European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology, and Management.' Statin-associated myopathy, with elevation of serum creatine kinase, is a rare but serious side effect of statins, affecting 1 per 1000 to 1 per 10,000 patients. Pre-clinical studies indicate that statins alter mitochondrial function, energy production, and muscle protein degradation. The authors propose the identification of statin-associated myopathy by typical symptoms such as muscle pain or aching and their temporal relationship with discontinuation and response to statin challenge. Further, they recommend using a maximally tolerated statin dose combined with a non-statin lipid-lowering compound in order to attain recommended LDL-cholesterol targets. To that end, at least three different statins should be tried, in order to reduce cardiovascular risk as much as possible. As the authors point out, further research into the underlying pathophysiological mechanisms is required to find future therapeutic options. Obviously, the novel PSK9 inhibitors will offer other options in the near future as they do not appear to be associated with such unwanted drug effects.

While it has been a known risk factor for myocardial infarction since the Surgeon General’s initial report in 1962, smoking remains an important health issue. Coronary computed tomography (CT) now allows for a precise and non-invasive assessment of coronary plaque burden in different types of smokers. In the first clinical research paper of this issue entitled 'Current but not past smoking increases the risk of cardiac events: insights from coronary computed tomographic angiography', James K. Min from the Weill Cornell Medical College in New York, USA evaluated coronary artery disease extent, severity, and major adverse cardiac events (MACE) in >15,000 never, past, and current smokers without known coronary artery disease undergoing coronary CT angiography. During almost 3 years of follow-up, current and past smokers had greater atherosclerotic burden than never smokers, as well as a higher prevalence of obstructive coronary artery disease. In addition, current smokers experienced higher MACE risk than never smokers, while past smokers did not. Even among matched individuals, current smokers had higher MACE risk including all-cause death, while past smokers did not. Among patients without known coronary artery disease undergoing coronary CT, current and past smokers had increased burden of atherosclerosis compared with never smokers; however, risk of MACE was heightened only in current smokers.

Coronary plaques and particularly vulnerable plaques may have different consequences depending on where they are located in the coronary vascular tree and what size of vessel is involved. This issue is addressed in the second clinical paper 'Influence of coronary vessel dominance on short- and long-term outcome in patients after ST-segment elevation myocardial infarction' by Arthur Scholte from the Leiden University Medical Center in The Netherlands. Coronary angiographic images of 1131 patients presenting with first ST-segment elevation myocardial infarction (STEMI) were retrospectively reviewed. After 5 years of follow-up, all-cause mortality was higher in patients with a left dominant system, compared with a right dominant and balanced system. Moreover, a left dominant system was an independent predictor for 30-day mortality and of the composite of reinfarction and cardiac death. In contrast, in patients surviving the first 30 days post-STEMI, coronary vessel dominance had no influence on long-term outcome. The authors conclude that a left dominant coronary artery system is associated with an increased risk of 30-day mortality and early reinfarction after STEMI.

The major unresolved question left is why atherosclerotic plaques rupture or develop endothelial denudation and in turn cause coronary vascular occlusion. It is known that inflammatory burst plays a crucial role, but the cells, their subgroups, and their interplay remain to be further clarified. Indeed, at least in experimental atherosclerosis, regulatory T cells (Tregs) exert anti-inflammatory and atheroprotective effects, while no data exist on Tregs and clonal restriction of T cells in patients with acute coronary syndromes (ACS). In the third manuscript, 'Clonal restriction and predominance of regulatory T cells in coronary thrombi of patients with
In STEMI patients, among T-cell subsets characterized by flow cytometry, Tregs (CD4+ CD25+ CD127(lo)) were twice as frequent in coronary thrombi compared with peripheral blood. Further, Tregs prevailed among T-cell subsets in coronary thrombi. To evaluate clonal restriction, genomic DNA was extracted from coronary thrombi and peripheral blood in order to evaluate T-cell receptor β chain diversity by means of Multi-N-plex PCR using a primer specific for all T-cell receptor β V gene segments and another primer specific for T-cell receptor β J gene segments. T-cell receptor diversity was reduced in thrombi compared with peripheral blood, with eight gene rearrangements in the T-cell receptor common in at least 6 out of 16 analysed coronary thrombi. Compared with age-matched healthy controls, T-cell receptor diversity was also reduced in peripheral blood of patients with ACS; these findings were independent of peripheral T-cell numbers. Thus, the authors provide novel evidence for a perturbed T-cell compartment characterized by clonal restriction in peripheral blood and coronary thrombi from patients with ACS. In the future Tregs may represent a novel therapeutic target, since enhancing this anti-inflammatory component of adaptive immunity may be beneficial in this context.

A limitation of research on plaque rupture is the fact that there are no animal models of the disease process. In the fourth paper ‘Elastin fragmentation in atherosclerotic mice leads to intraplaque neovascularization, plaque rupture, myocardial infarction, stroke, and sudden death’ Carole Van der Donckt and colleagues from the University of Antwerp in Belgium address this issue.15 The authors previously reported that elastin fragmentation due to the C1039G mutation in the fibrillin-1 gene promotes atherogenesis and provides an unstable plaque phenotype in apolipoprotein E-deficient (ApoE−/−) mice on a Western-type diet. In the present study, ApoE−/− Fbn1C1039G mice and ApoE−/− mice were fed a Western-type diet for up to 35 weeks. Compared with ApoE−/− mice, plaques of ApoE−/− fibrillin-1 C1039G−/+ mice exhibited a three-fold increase in necrotic core size, augmented T-cell infiltration, a decreased collagen I content, extensive neovascularization, intraplaque haemorrhage, and increased expression or activity of matrix metalloproteinase-2, -9, -12, and -13. Plaque rupture was independent of peripheral T-cell numbers. Thus, the authors provide novel evidence for a perturbed T-cell compartment characterized by clonal restriction and predominance of regulatory T cells in coronary thrombi of patients with acute coronary syndromes: the Task Force for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769–1818.

References


