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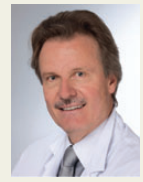
Atherosclerosis and CAD



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Atherosclerosis is the major disease process of cardiovascular medicine, leading to angina pectoris, myocardial infarction, and death. As stated many years ago by Rudolf Virchow, atherosclerosis is a chronic inflammation driven by cholesterol.[1] With the introduction of statins[2,3] guideliens from Europe and the USA[4] strongly recommend their use in such patients. Controversy only exists as to whether LDL cholesterol target levels or risk-adjusted dosing should be used in their management,[5] with the former advocated by the European Society of Cardiology and the latter by the American Heart Association.

In a *FAST TRACK* manuscript entitled '**Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study**'[6] by Stefan Windecker from the University Hospital Bern, accompanied an **Editorial** by Peter Libby from the Brigham and Women's Hospital in Boston,[7] this issue is addressed in 103 patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). The authors assessed the effects of a high-intensity statin therapy with rosuvastatin (40 mg/day) for 13 months using intravascular ultrasonography (IVUS) and radiofrequency ultrasonography (RF-IVUS), both well esthablished tools for the investigation of plaque burden, composition, and phenotype.[8] The primary IVUS endpoint was the change in percentage atheroma volume. After 13 months, LDL had decreased from a median of 3.29 to 1.89 mmol/L, and HDL cholesterol had slightly increased from 1.10 to 1.20 mmol/L (both $P < 0.001$). In line with LDL levels, the percentage atheroma volume significantly decreased by −0.9%. Patients with regression in at least one coronary segment were more common (74%) than those without (26%). In contrast, the necrotic core was unaffected, as was the number of RF-IVUS-defined thin cap fibroatheromas. The authors conclude that in STEMI patients who underwent primary PCI, high-intensity rosuvastatin therapy over 13 months is associated with regression of coronary atherosclerosis in non-infarct-related arteries without changes in RF-IVUS-defined necrotic core or plaque phenotype.

In the second manuscript, **'Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) Study'**[9] by Hyuk-Jae Chang *et al.* from the Yonsei University Severance Hospital in Seoul, South Korea, the prognostic value of coronary CT angiography (CCTA) according to coronary artery calcium scores (CACS) was investigated in asymptomatic patients. Indeed, although CCTA is used widely to diagnose or exclude coronary artery disease (CAD),[10] its predictive utility beyond that of CACS[11] and the Framingham risk score[12] among asymptomatic individuals remains uncertain. CCTA was performed and CACS determined in 3217 asymptomatic individuals without known CAD from a 12-centre, six-country observational registry. Participants were categorized by CACS as: 0–10, 11–100, 101–400, 401–1000, and > 1000. In the CCTA, the number of obstructed vessels—defined as the presence of > 50% luminal stenosis—was used to quantifiy the severity of CAD. During a median follow-up of 24 months, 58 composite endpoints occurred. Of note, the incremental prognostic value of CCTA over the Framingham risk score was obvious in individuals with a CACS > 100, but not among those with CACS ≤ 100. Among the participants with CACS > 100, the utility of CCTA for outcome prediction was evident among individuals whose CACS ranged from 101 to 400, while the observed predictive benefit was attenuated with increasing CACS. The authors conclude that among asymptomatic individuals CCTA provides incremental prognostic benefit for mortality and non-fatal myocardial infarction in those with moderately high CACS, but not for lower or higher CACS.

The third paper, entitled **'Risk model for estimating the 1-year risk of deferred lesion intervention following deferred revascularization after fractional flow reserve assessment'**,[13] by Jeremiah Peter Depta from the Brigham and Women's Hospital in Boston aims to develop a prediction model to estimate 1-year risk of deferred lesion intervention (DLI) for coronary lesions where revascularization was not performed following fractional flow reserve (FFR) assessment. Indeed, although deferred revascularization of coronary lesions following FFR[14,15] assessment in general has a low risk of future adverse cardiac events, the individual variability in risk may differ substantially and has not been previously investigated. The authors developed a prediction model for DLI in a cohort of 721 patients with 882 coronary lesions where revascularization was deferred based on FFR. DLI was defined as any revascularization of a lesion previously deferred following FFR. The final DLI model was developed using stepwise Cox regression and validated using bootstrapping techniques. An algorithm was constructed to predict the 1-year risk of DLI. During a follow-up period of 48 months, 18% of lesions deferred after FFR underwent DLI; the 1-year incidence of DLI was 5%, while the predicted risk of DLI varied

from 1% to 40%. The final Cox model included the FFR value, age, current or former smoking, history of CAD or prior percutaneous coronary intervention (PCI), multivessel CAD, and serum creatinine. The c statistic for the DLI prediction model was 0.66 [95% confidence interval (CI) 0.61–0.70]. The authors conclude that patients in which revascularization was deferred based on FFR have quite an important variation in their risk for DLI. A clinical prediction model consisting of five clinical variables and the FFR value can help to predict the risk of DLI in the first year following FFR assessment.

The last paper, '**Genetic deletion of the adaptor protein p66^{Shc} increases susceptibility to short-term ischaemic myocardial injury via intracellular salvage pathways**',[16] by Alexander Akhmedov from the Center for Molecular Cardiology at Zurich University, accompanied by an **Editorial** by Gerd Heusch from the Center for Internal Medicine in Essen, Germany,[17] investigated the role of the ageing gene p66^{shc} in experimental myocardial infarction. Indeed, genes involved in the regulation of life span have been implicated in cardiovascular disease.[1] Adult male p66^{Shc}-deficient (p66$^{Shc-/-}$) and C57Bl/6 wild-type (WT) mice were exposed to 30, 45, or 60 min of ischaemia and reperfusion (5 min, 15 min, or 24 h). Infarct size, systemic and intracardiac inflammation and oxidants, as well as cytosolic and mitochondrial apoptotic pathways were assessed. Following 30 min, but not 45 or 60 min of ischaemia, genetic p66^{Shc} deficiency was associated with larger infarcts. In WT mice, *in vivo* p66^{Shc} knock down by small interfering RNA (siRNA) with transient protein deficiency confirmed these findings. p66^{Shc} inhibition was not associated with any modification in post-infarction inflammation, oxidative burst, or cardiac vessel density or structure. However, in p66$^{Shc-/-}$ mice, activation of the protective and anti-apoptotic RISK and SAFE pathways was blunted, and mitochondrial swelling and cellular apoptosis via the caspase-3 pathway increased compared with the WT. The authors conclude that—contrary to initial expectations—genetic deletion of p66^{Shc} increased rather than decreased the susceptibility to myocardial injury in response to short-term ischaemia and reperfusion in mice. It is of note that the expression of p66^{Shc} is reduced in patients with acute coronary syndromes.[18] Whether the acute downregualtion of p66^{Shc} contributes to myocardial injury in patients with acute coronary syndromes needs appropriate clnical studies.

This issue is complemented by two clinical reviews on the subject. The first, entitled **'Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management'**,[19] is by Giampaolo Niccoli from the Catholic University of the Sacred Heart in Rome. This under-recognized condition does indeed deserve the attention of our readers. The authors note that myocardial infarction with no obstructive coronary atherosclerosis (MINOCA) is a syndrome with different causes. Its prevalence is estimated as between 5% and 25% of all myocardial infarctions. The prognosis of MINOCA appears to vary considerably depending on the underlying cause. Upon presentation, clinical history, echocardiography, coronary angiography, and ventriculography are the first-line diagnostic examinations. Nevertheless, additional tests such as cardiac magnetic resonance imaging (MRI),[20,21] among others, are required in order to establish its specific cause, thus allowing an appropriate risk stratification and treatment. The authors review the pathogenesis, diagnosis, prognosis, and therapy of MINOCA, and propose a algorithm for its management.

The second clinical review, '**Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatological conditions**',[22] by Justin Mason from Imperial College, London draws our attention to a variety of systemic inflammatory rheumatic diseases that are associated with an increased risk of premature cardiovascular disease. Indeed, while LDL, particularly in its oxidized form, induces a chronic inflammatory process characteristic of atherosclerosis, inflammation in other parts of the body may also promote plaque formation.[23] Although this recognition has stimulated intense basic science and clinical research, the precise nature of the relationship between local and systemic inflammation, their interactions with traditional cardiovascular risk factors, and their role in accelerating atherogenesis remain unresolved. The spectrum of rheumatic diseases has unique attributes that may influence cardiovascular events, but the understanding of the positive and negative influences of individual anti-inflammatory therapies is still limited. The development of preventative and disease-modifying strategies in these patients can only occur in close collaboration between basic scientists, cardiologists, and rheumatologists, and hopefully this review will foster this process.

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

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