Novel risk markers and mediators in coronary disease and stroke

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For research and clinical application, the central role of oxidative signalling in cardiovascular pathophysiology \(^1\)\(^{-6}\) positions measures of the redox state conceptually as ideal biomarkers. Despite this overwhelming biological plausibility, no redox biomarker is currently in clinical use, nor have antioxidants provided any clinical benefit in large trials.

Recent insights into the mechanistic complexities of redox signalling may lead to the identification of clinically useful markers. Advances with the greatest potential include assays measuring post-translational oxidative modifications of essential proteins affecting cellular function. However, analytical issues, including the relative instability of redox-modified products, remain a major technical challenge. In a timely Clinical Review article entitled ‘Redox biomarkers in cardiovascular medicine’, Gemma Alexandra Figtree from the University of Sydney in Australia reviews this promising area and discusses both established and recently identified biomarkers of redox signalling. Despite the current lack of redox biomarkers in clinical application, the integral role of reactive oxygen species (ROS) in the pathogenesis of cardiovascular disease provides a strong incentive for continued research efforts in this field. \(^7\) Epidemiological studies suggest a relationship between pathological events during foetal development and future cardiovascular risk. To describe this phenomenon, the term ‘foetal programming’ has been coined. In a second Clinical Review article ‘Cardiovascular dysfunction in children conceived by assisted reproductive technologies’ by Urs Scherrer from the University Hospital of Bern in Switzerland, \(^8\) emerging evidence indicating that assisted reproductive technologies represent a novel, hitherto unrecognized example of foetal programming is discussed. Of note, the use of assisted reproductive technologies is growing exponentially, and 2–5% of children are now born with the help of this procedure. Assisted reproductive technologies may modify the cardiovascular phenotype in two ways: first, assisted reproductive technologies involve manipulation of the early embryo, which is exquisitely sensitive. These technologies alter vascular and cardiac function in children, and induce epigenetic alterations. Secondly, assisted reproductive technologies markedly increase the risk of foetal insults that augment cardiovascular risk in naturally conceived individuals. Given the young age of the assisted reproductive technologies population, it will take another decade before their outcome can be looked at. It appears, however, that assisted reproductive technologies will emerge as a novel cardiovascular risk factor. There is an urgent need to better understand the mechanisms of alterations of the cardiovascular phenotype induced by assisted reproductive technologies, to improve the procedure, using assisted reproductive technologies parsimoniously, and not abandoning medicine’s fundamental principle of doing no harm.

Plasma levels of cholesterol are determined by its hepatic production, its uptake, and clearance by LDL receptors and by the activity of the Niemann–Pick C1 Like 1 (NPC1L1) protein, the transporter responsible for cholesterol uptake from the intestine into enterocytes and from the bile into hepatocytes. In the first clinical research paper, Anne Tybjærg-Hansen from the Rigshospitalet in Copenhagen, Denmark reports on ‘Genetic variation in the cholesterol transporter NPC1L1, ischaemic vascular disease, and gallstone disease’. \(^9\) The authors tested the hypothesis that genetic variations in NPC1L1 mimic the effects of ezetimibe, \(^10\) and are associated with a reduced risk of ischaemic vascular disease and an increased risk of symptomatic gallstone disease.

To that end, they included 67 385 individuals from the general population. Of these, 5255 and 3886 individuals developed ischaemic vascular disease or symptomatic gallstone disease, respectively. With an increasing score of four common NPC1L1 variants, LDL-cholesterol decreased stepwise up to 3.5% and total cholesterol up to 1.9%. Interestingly, the cumulative incidence of ischaemic vascular disease decreased, while that of symptomatic gallstone disease increased with increasing genotype score. The authors conclude that genetic variations in NPC1L1 are associated with a reduction in risk of ischaemic vascular disease due to a reduction in LDL-cholesterol, but an increased risk of gallstone disease. This is in line with the fact that the NPC1L1 inhibitor ezetimibe protects against ischaemic events [and accordingly is recommended in the European Society of Cardiology (ESC) Guidelines \(^11\) and by the European Atherosclerosis Society \(^12\), but raises the question of whether long-term treatment increases the risk of gallstone disease. The manuscript is accompanied by a comprehensive Editorial by Heribert Schunkert from the Deutsches Herzzentrum in Munich, Germany, which puts the genetics of this paper into a broader perspective. \(^13\)

Orthostatic hypotension is a known cause of falls and syncope, \(^14\) but it remains uncertain whether or not it represents an unrecognized cardiovascular risk factor. In the second clinical research paper, ‘Cardiovascular morbidity and mortality related to...’
Stroke is a devastating event for patients and their families, and most commonly related to age, uncontrolled hypertension, or atrial fibrillation. However, it is also known as a complication of cardiac procedures. In the third clinical research manuscript entitled ‘Stroke following percutaneous coronary intervention: type-specific incidence, outcomes, and determinants seen by the British Cardiovascular Intervention Society 2007–2012’, Chun Shing Kwok and colleagues from the University of Manchester in the UK evaluated temporal changes in stroke complications and their association with mortality and MACE outcomes in a national cohort of 426,046 patients undergoing percutaneous coronary interventions (PCI) in England and Wales. Only 436 (0.1%) of the patients sustained an ischaemic stroke or transient ischaemic attack, and 0.03% a haemorrhagic stroke. Both complications increased from 0.67 to 1.14 per 1000 patients between 2007 and 2012, whilst haemorrhagic strokes decreased from 0.29 to 0.15. After adjustment for baseline clinical and procedural demographics, ischaemic stroke was independently associated with both 30-day mortality, with an odds ratio of 4.92, and in-hospital MACE, with an odds ratio of 3.1. An even greater impact on prognosis was observed with haemorrhagic complications, with an odds ratio of 13.87 for 30-day mortality and of 13.5 for in-hospital MACE. The authors conclude that the incidence of ischaemic strokes has increased over time, whilst that of haemorrhagic strokes has decreased, driven through changes in clinical, procedural, drug treatment, and demographic factors. Both ischaemic and haemorrhagic strokes are rare, but they have devastating complications, with high 30-day mortality and in-hospital MACE rates. These findings are put into context by an excellent Editorial by Stefan James from the Mayo Clinic in Rochester, Minnesota, USA.

Finally, in the fourth Basic Science paper entitled ‘Post-ischaemic silencing of \( p66^{\text{Shc}} \) reduces ischaemia/reperfusion brain injury and its expression correlates to clinical outcome in stroke’, Giovanni Camici and colleagues from the University of Zurich in Switzerland report on a novel, so far experimental treatment of ischaemic stroke by genetic silencing of the adaptor protein \( p66^{\text{Shc}} \). In a previous study published in this Journal, the authors showed that \( p66^{\text{Shc}^{-/-}} \) knockout mice are protected from ischaemia/reperfusion injury in the brain. Using transient middle cerebral artery occlusion, small interfering RNAs targeting \( p66^{\text{Shc}} \) were injected intravenously prior to reperfusion, as would be the case in a clinical setting. Interestingly, post-ischaemic \( p66^{\text{Shc}} \) silencing preserved blood—brain barrier integrity, resulting in improved stroke outcome, as identified by smaller lesion volumes, decreased neurological deficit, and increased survival. Experiments on primary human brain microvascular endothelial cells confirmed that silencing of \( p66^{\text{Shc}} \) preserves claudin-5 protein levels during hypoxia/reoxygenation by reducing nicotinamide adenine dinucleotide phosphate oxidase activity and reactive oxygen species production. An important translational finding was that in peripheral blood monocytes of patients with acute ischaemic stroke, \( p66^{\text{Shc}} \) gene expression was transiently increased and the increase correlated with short-term neurological outcome. Thus, post-ischaemic silencing of \( p66^{\text{Shc}} \) directly prior to reperfusion improves stroke outcome in mice, while the expression of the \( p66^{\text{Shc}} \) gene correlates with short-term outcome in patients with ischaemic stroke. Massimo Volpe from the University of Rome Sapienza in Italy discusses the study and its clinical potential in an accompanying Editorial.

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


