Acute coronary syndromes: mechanisms, reperfusion injury, antithrombotic therapy, and current outcomes

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The management and, as a consequence, the outcome of acute coronary syndromes or ACS have improved impressively over the last decades,1 but they remain the most important cause of re-hospitalization, re-interventions, heart failure, and death.2 To reduce infarct size further and thus ameliorate clinical outcome, current guidelines recommend early detection with high-sensitive troponin assays, ECG, and imaging in those with non-ST segment myocardial infarction (NSTEMI)3 and, if required, urgent primary percutaneous coronary intervention (PCI), particularly in STEMI.4 In STEMI, reperfusion after longer periods of ischaemia may cause myocardial injury. Thus, based on experimental findings, cardioprotection against reperfusion injury, with either mechanical (ischaemic post-conditioning, remote ischaemic pre-conditioning, therapeutic hypothermia, and hypoxaemia) or pharmacological interventions (atrial natriuretic peptide, cyclosporine A, and exenatide), has been investigated. Cardiac stem cell treatment also has been suggested to reduce infarct size and negative remodelling of the left ventricle that may further improve symptoms and prognosis. Fabrizio Montecucco et al. from the University of Genoa in Genoa, Italy review these topics in their article ‘Pathophysiology of ST-segment elevation myocardial infarction: novel mechanisms and treatments’.5

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor is essential in the treatment of ACS patients immediately before and after primary PCI.6–8 In recent years, the most appropriate timing for initiation and particularly the duration of P2Y12 receptor inhibition has been at the centre of interest. In their review ‘Pre-treatment with P2Y12 inhibitors in ACS patients: who, when, why, and which agent?’ Dirk Sibbing and colleagues from the Deutsche Herzzentrum München in Germany9 discuss this issue in great depth. One issue is the usefulness of pre-treatment with P2Y12 receptor inhibitors upstream of coronary angiography and PCI. Recently, two randomized trials evaluated the value of pre-treatment with disappointing results—one in NSTEMI, i.e. the ACCOAST trial10 and in a second one in STEMI, i.e. the ATLANTIC trial.11 Neither of these, however, answered all questions. Indeed, given the recent approval of the intravenous P2Y12 inhibitor cangrelor, the issue got a new twist.12,13 The authors evaluate and discuss the available evidence regarding the value of pre-treatment with the now available four oral and intravenous P2Y12 inhibitors that can be administered to patients in whom coronary angiography followed by a possible primary PCI is planned.

As an extension of the review by Montecucco et al., C. Michael Gibson and colleagues from the PERFUSE Study Group tested a cell-permeable peptide, i.e. MTP-131, that experimentally preserves the integrity of cardiolipin, enhances mitochondrial energetics, and improves myocyte survival during reperfusion. In their EMBRACE STEMI study: a Phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention,14 they report the results of a multicentre, randomized, double-blind Phase 2a trial that evaluated the efficacy and safety of MTP-131 compared with placebo infused at a rate of 0.05 mg/kg/h for 1 h among patients with a first anterior STEMI undergoing primary PCI for a proximal or mid left anterior descending artery occlusion. The authors conclude that administration of MTP-131—as the case for many molecules studied previously in this context15–17—was not associated with a reduction in the primary endpoint of infarct size by creatine kinase (CK)-MB area under the curve over 72 h nor was it associated with an improvement in magnetic resonance imaging (MRI), angiographic, electrocardiographic, or clinical outcomes.

The progress made in management of ACS even in the last years is remarkable.18–20 Real-world data from Switzerland are provided in the paper ‘Temporal trends in the treatment and outcomes of elderly patients with acute coronary syndrome’ by Paul Erne on behalf of the AMIS Plus Investigators.21 They prospectively analysed between 2001 and 2012 the use of guideline-recommended therapies and in-hospital outcomes among 13,662 ACS patients 70 years of age or older. Between the first and last 4 years, the use of guideline-recommended drugs and of primary PCI use increased from 44% to 70% of older ACS patients. Concomitantly, in-hospital mortality decreased from 12% to 10%, and major adverse cardiac and cerebrovascular events from 14% to 11%. Primary PCI was used increasingly and successfully in older and co-morbid patients. The authors conclude that over a recent 12-year period, use of guideline-recommended therapies in ACS increased and in-hospital outcomes improved.
Antithrombotic therapy is essential for outcome of primary PCI, particularly in STEMI. As such, the HORIZONS and other trials found a survival advantage for bivalirudin over heparin plus glycoprotein IIb/IIIa blockers during primary PCI for STEMI. However, subsequent studies have produced divergent findings. In the third paper, entitled ‘Bivalirudin, glycoprotein inhibitor, and heparin use and association with outcomes of primary percutaneous coronary intervention in the UK’, Alexander Sirker and colleagues from University College London Hospitals NHS Foundation Trust in the UK investigated this issue in the largest population so far using the UK PCI registry of 61,136 patients. Unadjusted data demonstrated near-identical survival curves for bivalirudin and heparin plus glycoprotein IIb/IIIa blocker groups. Of note, early and late mortality was higher in patients treated with heparin alone, but this group also had a markedly higher baseline risk. After propensity matching, the bivalirudin vs. heparin plus glycoprotein IIb/IIIa blocker groups had still similar adjusted mortality. Patients treated with heparin alone continued to show higher mortality, although the effect size was considerably diminished at 30 days, with an odds ratio of 1.17–1.24. Thus, in STEMI patients undergoing primary PCI, short- or medium-term mortality was similar regardless of whether bivalirudin or heparin plus glycoprotein IIb/IIIa blockers were used. The paper is accompanied by an Editorial by Petr Widimsky from the Charles University in Prague, Czech Republic.

Growth differentiation factor 15 (GDF-15) appears to predict death and cardiovascular events in patients with different cardiovascular conditions, but confirmation in truly large prospective cohorts is missing. In the fourth paper ‘Growth differentiation factor 15 level predicts major bleeding and cardiovascular events in patients with acute coronary syndromes: results from the PLATO study’, Emil Hagstrom and the PLATO investigators studied the independent associations between GDF-15 levels and major bleeding, the extent of coronary lesions, and events in 16,876 patients with ACS. During a 12-month follow-up, GDF-15 levels were related to extent of coronary artery disease and to all types of non-coronary artery bypass (CABG)-related major bleeding, spontaneous myocardial infarction, stroke, and death. After adjusting with Cox proportional hazards models, one standard deviation increase in GDF-15 remained associated with increased risk of major bleeding, with a hazard ratio of 1.37 and with a similar increase in risk across different bleeding locations. For the same increase in GDF-15, the hazard ratio for the composite of cardiovascular death, infarction, and stroke was 1.29, 1.41 for cardiovascular death, 1.41 for all-cause death, 1.15 for spontaneous infarction, and 1.19 for stroke. The authors conclude that in ACS, higher levels of GDF-15 are associated with an increased risk of major non-CABG-related bleeding, spontaneous infarction, and stroke as well as mortality. Thus, in ACS GDF-15 seems to improve risk stratification beyond established risk factors. The paper is accompanied by an Editorial by Kai C. Wollert from the Hannover Medical School in Germany.

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

References


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