The year in cardiology 2014: acute coronary syndromes

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Preamble

This review provides an overview of key findings published in 2014 on the pathophysiology, early diagnosis, prognosis, and acute and long-term treatment of acute coronary syndromes (ACS). A perspective on future research is provided at the end. We did not report on the progress made with mechanical interventions as this topic will be covered in another review. As so many studies have been published on ACS and because of the restrictions imposed by the journal, the selected papers unavoidably reflect the interests and personal opinion of the authors to a certain extent. As in many other studies ACS covers all types of non-ST-segment elevation and ST-segment elevation myocardial infarction (NSTE-MI and STEMI). Little data have been provided on unstable angina patients in recent years. The increasing use of high-sensitivity troponins (hsTn) makes the diagnosis of unstable angina very unusual if not impossible.

Pathophysiology, early diagnosis, and risk stratification

Plaque rupture, plaque erosion, and functional alterations of coronary circulation are responsible for ACS. Niccoli et al.1 found that these different mechanisms, identified by optical coherence tomography, were associated with different patterns of biomarker levels. Indeed, patients with plaque rupture displayed a marked elevation of C-reactive protein suggesting a systemic active inflammatory process that progressively leads to cap thinning and rupture. Patients with erosion, on the other hand, exhibited higher myeloperoxidase levels, which might trigger thrombus formation at the site of an eroded plaque expressing hyaluronan. Finally, cystatin-C levels were higher in patients who did not exhibit fissure or erosion of the culprit plaque, thus suggesting functional mechanisms operating in epicardial coronary arteries or in the microcirculation. Biomarkers able to identify the mechanism of instability operating in the individual patient might open a new way to personalized forms of treatment. With regard to the role of inflammation in ACS, Klingenberg et al.2 have provided novel evidence for a perturbed T-cell compartment characterized by clonal restriction in peripheral blood and coronary thrombi from patients with ACS, thus confirming the important role of adaptive immunity in coronary instability. Notably, they found that regulatory T cells (Treg) prevailed among T-cell subsets identified in coronary thrombi. It is likely that the increase in Treg in coronary thrombi reflects a local compensatory response to attenuate inflammation in the surrounding pro-inflammatory milieu characterized by elevated concentrations of pro-inflammatory cytokines in coronary blood distal to the occluding coronary thrombus. The concept of enhancing antigen-specific Treg to diminish vascular inflammation in ACS by immunotherapy is an appealing therapeutic perspective. With regard to functional alterations of the coronary circulation, Nihei et al.3 found a remarkable correlation between Rho kinase activity in circulating leucocytes and severity of acetylcholine-induced epicardial coronary constriction in patients with vaso-spastic angina, suggesting that this is a potentially useful biomarker of disease activity in these patients. This study also confirms that coronary spasm is caused by a dysfunction of smooth muscle cells, where enhanced Rho kinase activity increases the susceptibility to constrictor stimuli, rather than by endothelial dysfunction.

With regard to early diagnosis in a randomized controlled trial in 902 patients with low-to-intermediate risk and suspected ACS admitted to the emergency department, Möckel et al.4 compared a strategy based on combined measurements of copeptin and hsTn with a standard strategy. The percentage of patients discharged from the emergency department was higher (67.6% vs. 12.0%, P < 0.001) and the median length of stay was shorter (4 h vs. 7 h; P < 0.001) while the incidence of major cardiovascular events was similar in the two groups. Thus, the combined measurement of copeptin and hsTn might become a cost-effective approach for ruling out ACS, although ongoing studies are also testing the potential advantage of new strategies entirely based on hsTn measurements. In another study carried out in 36 patients with Takotsubo cardiomyopathy (TTC), 27 STEMI patients, and 28 healthy controls, Jaguszewski et al. found that a unique signature comprising miR-1, miR-16,
miR-26a, and miR-133a differentiated TTC from healthy subjects [area under the curve (AUC) 0.835; \( P < 0.0001 \)] and from STEMI patients (AUC 0.881; \( P < 0.0001 \)) (Figure 1). This study is the first to identify a signature of miRNAs as a robust biomarker to distinguish TTC from STEMI patients. Notably, the significant up-regulation of stress- and depression-related miRNAs suggests a close connection of TTC with neuropsychiatric disorders. A topic of growing interest is represented by patients with ACS and no obstructive coronary artery disease (CAD). In a post hoc analysis of the ACUITY trial using propensity matching, Planer et al. identified 117 patients with no obstructive CAD and 331 patients with obstructive CAD and NSTEMI but no significant baseline differences. In this matched cohort, overall 1-year mortality was significantly higher in patients with no obstructive CAD (5.2% vs. 1.6%; \( P = 0.04 \)), driven by a higher non-cardiac mortality. Conversely, recurrent MI and unplanned revascularization rates were significantly higher in patients with obstructive CAD. This study highlights the need for a careful prognostic assessment of patients with NSTEMI and no obstructive CAD as this subset (about 10% of patients admitted with NSTEMI) portends a prognosis worse than previously appreciated. This subset is probably heterogeneous including patients with vaso-spastic angina, unstable microvascular angina, myocarditis, and coronary microembolization. The haemodynamic, vascular, inflammatory, and myocardial oxidant stress mechanisms promoted by sleep apnoea may adversely influence the infarcted and ischaemic myocardium as well as myocardial healing. However, there are limited data on the complex relationship between infarct healing, left ventricular remodelling, and sleep apnoea in patients with acute MI. In one study Buchner et al. (Figure 2) found that patients with acute MI and sleep apnoea had significantly less salvaged myocardium, smaller reduction in infarct size within 3 months after acute MI, a larger final infarct size, and a lower final left ventricular ejection fraction assessed by cardiac magnetic resonance. In a multivariable analysis,
Antiplatelet and anticoagulant therapy

The advantages of new P2Y2 antagonists have been explored in clinically relevant subgroups of patients. Data from PLATO indicate that the benefit of ticagrelor over clopidogrel is consistent in reducing ischaemic events and total mortality in NSTE MI independent of actually performed revascularization. Similarly, the efficacy and safety profile of ticagrelor was the same in the men and women participating in PLATO. The significant mortality reduction seen in PLATO is not fully explained by the actions on the P2Y2 receptor. There is now evidence that ticagrelor inhibits adenosine uptake by red blood cells. This property of ticagrelor may explain its so-called pleiotropic effects (e.g. vasodilation, infarct size reduction). The clinical relevance of these findings is still uncertain. In the ATLANTIC study, no improvement in reperfusion was shown with pre-hospital administration of ticagrelor in STEMI patients when compared with in-hospital administration. However, less stent thrombosis was observed in the pre-hospital group. The duration of antiplatelet therapy in ACS patients who got a drug-eluting stent (DES) remained associated with a higher risk of death, stroke, or reinfarction. At the annual scientific sessions of the AHA in Chicago in November 2014 several studies on the duration of dual antiplatelet therapy after DES implantations were presented. Although post-ACS patients were included in these studies the great majority were stable CAD patients. In the largest study, the DAPT study, patients with a DES who tolerated well 1 year of dual antiplatelet therapy had significantly less stent thrombosis and myocardial infarction when treated for 30 instead of 12 months. However, death and bleeding complications occurred more frequently with prolonged treatment. It is unlikely that the results of these studies will change the current recommendations for the duration of dual antiplatelet therapy after ACS.

In many hospitals bivalirudin has replaced heparin especially for primary percutaneous coronary intervention (PCI) mainly based on the results HORIZONS-AMI study showing significantly reduced bleeding rates and lower 30-day mortality with bivalirudin alone when compared with heparin plus a GPIIb/IIIa antagonist. The benefit of bivalirudin for primary PCI was seriously challenged by the recent single centre trial HEAT-PCI in which GPIIb/IIIa antagonists were used for bail-out only in both arms. Fewer ischaemic events occurred with heparin and, surprisingly and in contrast with all previous trials, no reduction in bleeding complications was found with bivalirudin. In the EUROMAX study in patients transported for primary PCI an increase in stent thrombosis with bivalirudin (with bail-out use of GPIIb/IIIa antagonists < 10%) was also observed however with a significant reduction in bleeding complications when compared with heparin only plus GPIIb/IIIa antagonists restricted to bail-out (25%) or heparin plus routine GPIIb/IIIa antagonists. The risk of both bleeding and stent thrombosis seems with bivalirudin seems to largely determined by the concomitant use of GPIIb/IIIa antagonists.

Reperfusion and revascularization

Although major efforts have been made to reduce the door-to-balloon time further reductions in in-hospital mortality have not been observed over the last years indicating that other components of the total ischaemic time need to be targeted. A strategy that might be incorporated in the pre-hospital setting is the administration of a fibrinolytic agent in early (< 3 h) presenting STEMI patients who cannot get PCI within 1 h as studied in STREAM. The 1-year mortality of STREAM showed almost identical mortality rates in the primary PCI and pharmaco-invasive arms (with halve dose tenecteplase in the elderly which reduced the risk of intracranial bleeding from 1.0 to 0.5%). An interesting survey using data from 155 818 patients in the Myocardial Ischaemia National Audit Project (MINAP) found that older patients were incrementally less likely to receive secondary prevention medicines (including aspirin, ACE inhibitors, and statins) and intensive management for both STEMI and NSTE MI (Figure 3). Furthermore, in STEMI patients ≥85 years, 55% received reperfusion compared with 84% in those aged 18 to 65 [OR 0.22 (95% CI 0.21, 0.24)]. Not receiving intensive management was associated with worse survival in all age groups. These and other findings highlight the requirement to improve standard of care in the growing population of older patients with ACS. With regard again to inequalities, a cross-sectional study based on aggregated country-level data on the use of reperfusion therapy in patients admitted with STEMI during 2010 or 2011 in 37 European countries found that the number of primary PPCIs varied between countries, ranging from 23 to 884 per million.
The mean population served by a single primary PCI centre with a 24-h service 7 days a week ranged from 31 300 inhabitants per centre to 6 533 000 inhabitants per centre.

Countries in Eastern and Southern Europe reported a substantial larger number of STEMI patients not receiving any reperfusion therapy. It is well accepted that coronary revascularization in high-risk NSTEMI patients is beneficial. The selection of patients for revascularization is usually based on clinical parameters, ECG and
biomarkers such as hsTn. In an interesting study the use of fractional flow reserve (FFR) has been compared with standard angiography (without FFR) in 350 NSTEMI patients. The performance of FFR resulted in a significantly lower rate of coronary revascularization not only in the acute phase but also at 1 year.\textsuperscript{22} No significant differences in clinical outcomes or quality of life were found between the two strategies.

**Long-term outcomes**

Statins are standard therapy following ACS. Whether the concept ‘the lower the better’ is still valid at very low LDL levels has been tested in the IMPROVE-IT study.\textsuperscript{23} An incremental clinical benefit (fewer ischaemic events) was observed at 7 years follow-up in ACS patients with LDL levels 50–125 mg/dL (or 50–100 mg/dL if on prior lipid lowering therapy) with simvastatin 40 mg plus ezetimibe 10 mg vs. simvastatin 40 mg alone. In the combined treatment arm the mean LDL level during the course of the study was 53 mg/dL. Ezetimibe was very well tolerated.

At the present it remains unproven if anti-inflammatory agents may further improve long-term outcomes after ACS. A large number of studies are still ongoing. Two have been published in 2014: the inhibitors of Lp-PLA2 and sPLA2 (darapladib and varespladib, respectively) have failed to show a benefit after ACS in two large randomized trials.\textsuperscript{24,25} Stronger anti-inflammatory agents such as losmapimod (inhibitor of p38MAPK) and colchicine are currently being studied in patients post ACS.\textsuperscript{26,27} Similarly, studies targeting HDL (reconstituted HDL) in ACS patients are ongoing. In an interesting study the clinical outcomes after ACS in UK and Sweden were compared using standardized national registries. Important differences in the use of beta-blockers and primary PCI between the two countries were observed. After case-mix standardization an excess mortality of 37% at 30 days in the UK was found when compared with Sweden. Obviously, comparisons of clinical outcomes within and between countries using standardized registries might help to improve health care.\textsuperscript{28} This study illustrates how comparative effectiveness research can be performed by using standardized data sets. How to develop these standardized registries was extensively explained by Hendel et al.\textsuperscript{29}

**Perspectives**

It is clear that ACS will remain the first clinical manifestation of coronary atherosclerosis in the great majority of patients and therefore will remain a key topic of future research. Major progress has been made in the understanding of its pathophysiology as well as in diagnosis and treatment of ACS, yet many patients even in Western countries do not get the benefit of it. Better organization of pre-hospital and emergency care with a greater involvement of cardiologists needs to be implemented. Further research on mechanisms, biomarkers and risk factors may result in a more personal and therefore more effective and safer treatment. A refinement of our antithrombotic strategies in the acute and chronic phase is also needed. Numerous combinations of oral antithrombotic agents can be prescribed at discharge. Not all of them can be tested in double blind randomized studies. Future guidelines on ACS will have to incorporate also data from comparative effectiveness research performed via electronic health records. Long-term mortality rates remain high and it is unclear whether adding an anti-inflammatory agent or another antithrombotic (on top of aspirin) after 1 year may improve survival. Simple large scale outcome studies will be needed.

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