The Year in Cardiology 2013: acute coronary syndromes

Christian W. Hamm1,2* and Filippo Crea3

1Kerckhoff Heart and Thoraxcenter, Bad Nauheim, Germany; 2Medical Clinic I, University of Giessen, Giessen, Germany; and 3Department of Cardiovascular Sciences, Catholic University, Roma, Italy

Received 15 October 2013; revised 12 November 2013; accepted 27 November 2013

Patients presenting with acute coronary syndromes (ACS) remain a challenging medical condition with potential in improving outcome despite major advances over recent years. During the year 2013, progress has been made with respect to a better understanding of the underlying mechanisms and diagnosing ACS. In addition, new studies provided fundamental insights the optimal management, particularly with respect to the best antithrombotic regimen.

------------------

Keyword
Acute coronary syndromes

Pathophysiology

While it is well established that obesity is a risk factor for cardiovascular events in subjects without pre-existing disease, several recent studies have highlighted the ‘obesity paradox’ characterized by a better outcome of obese subjects with established cardiovascular disease when compared with lean subjects. In particular, Angerås et al. extracted 64,436 patients who underwent coronary angiography due to acute coronary syndrome (ACS) from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). In this large and unselected group of patients with ACS, the relation between body mass index and mortality was U-shaped, with the nadir among overweight or obese patients and underweight and normal-weight patients having the highest risk. These data suggest the presence of obesity-related protective mechanisms, which may offset the increased risk given by obesity-related metabolic alterations. Potential protective mechanisms might be enhanced release of adipokines and of progenitor endothelial cells as well as a potential anti-arrhythmic effect of fat, identified in experimental models. A better knowledge of these protective mechanisms operating in obese patients might open the way to new forms of treatment.

In another study, Niccoli et al. highlighted a ‘diabetes paradox’. They compared the angiographic findings in patients with or without diabetes at the time of a very first ACS, and found that coronary atherosclerosis extent and severity were much greater in those with diabetes in spite of more advanced atherosclerosis. Such protective factors might be represented by better collateral development and by a higher prevalence of a calcific rather than lipidic plaque phenotype in diabetic patients as well as by hyperglycaemia-associated inhibition of matrix metalloproteinases observed in experimental studies.

With regard to the mechanisms of coronary thrombus formation, Pessi et al. found bacterial DNA typical for endodontic infection, mainly oral viridans streptococci, in 78.2% of coronary thrombus aspirates obtained from patients with ST-elevation acute myocardial infarction (STEMI). This observation, however, does not allow establishing whether the bacteria were from living bacteria inside coronary atheroma or whether they were simply fragments from bacterial DNA engulfed by phagocytic cells from the circulation without any pathological significance. These findings, nevertheless, suggest to investigate whether improvements in dental health and dental care could be a major goal of preventive efforts.

Early diagnosis and risk stratification

A diagnostic challenge worldwide is a rapid rule out of acute myocardial infarction (AMI) among patients admitted to the emergency department with suspected ACS. In a multicycle...
study, Maisel et al.\textsuperscript{4} enrolled 1967 patients with chest pain presenting to an emergency department within 6 h of pain onset and measured copeptin (the C-terminal portion of the arginine vasopressin precursor) and high-sensitivity Troponin I (cTnI) levels at admission. Acute myocardial infarction was the final diagnosis in 156 (7.9%) patients. A negative copeptin and cTnI at baseline ruled out AMI for 58% of patients, with a negative predictive value of 99.2%. Of note, AMI not detected by the initial cTnI alone was picked up by copeptin using a cut-off value of $>14$ pmol/L in 23 (72%) of 32 patients. These findings have recently been confirmed by M. Moeckel at the 2013 Annual Meeting of the European Cardiac Society (unpublished data). Thus, the combined measurement of copeptin and high-sensitivity troponin might become a cost-effective approach for the rule out of ACS in patients presenting suspected chest pain.

In an innovative study, Wauters et al.\textsuperscript{5} evaluated whether 23 susceptibility loci, known to be associated with coronary artery disease, also predispose to recurrent MI or cardiac death following an ACS (Figure 1). Interestingly, they found that among 2099 ACS patients enrolled in the Global Registry of Acute Coronary Events (GRACE), C-allele carriers of the rs579459 variant, which is located upstream of the ABO gene and correlates with blood Group A, were independently associated with recurrent AMI and with recurrent AMI or cardiac death within 5 years after the index ACS. Although external replication is needed to confirm these early findings and to better assess interactions with covariates, this study opens the way to the utilization of genetic assessment in the risk stratification of ACS.

Barthel et al.\textsuperscript{6} tested whether the respiratory rate provides prognostic information and how this information compares with that of established risk assessment in 941 STEMI patients. On multivariate analysis, the respiratory rate was an independent predictor of death. In particular, among patients with a high GRACE risk score ($\geq 120$), 5-year mortality exceeded 50% among those with left ventricular ejection fraction (LVEF) of $\leq 35\%$ and respiratory rate of $\geq 20$ breaths/min, whereas it was $<10\%$ among those with an LVEF of $>35\%$ and a respiratory rate of $<20$ breaths/min. This study highlights how simple and inexpensive clinical observations can be as important in daily practice as the utilization of expensive biomarkers and bio-imaging techniques.

In a single-centre study, Link et al.\textsuperscript{7} investigated biomarkers of risk in the important subset of patients with cardiogenic shock and found that Angiopoietin-2 levels independently predicted a 1-year mortality rate. These findings, if confirmed in larger patient populations in multicentre studies, are potentially important for the early identification of very high-risk patients who might benefit of intra-aortic balloon counterpulsation or of LV assistance devices. More importantly, Angiopoietin-2 might become a therapeutic target; indeed, it inhibits the binding of Angiopoietin-1 to Tie-2, thus resulting in impaired endothelial integrity, which appears to play an important pathogenetic role in cardiogenic shock.

### Stem cells

In the TIME trial, Traverse et al.\textsuperscript{8} enrolled 120 patients with an LVEF $\leq 45\%$ after successful primary percutaneous coronary intervention (PCI) of anterior stent thrombosis (ST)-elevation AMI. Patients were randomized to intracoronary infusion bone marrow mononuclear cells or placebo (randomized 2 : 1) administered at Day 3 or 7 (randomized 1 : 1) after PCI. The administration of intracoronary bone marrow mononuclear cells at either 3 or 7 days after the event had no significant effect on recovery of global or regional left ventricular function compared with placebo. The design of TIME was based on the previous data, suggesting that the timing of cell delivery may be critical. Although the field of cell therapy in cardiovascular disease has potential for identifying beneficial treatments, this study is consistent with the possibility that bone marrow mononuclear cells are not effective at improving LV function when delivered into the immediate post-STEMI myocardial environment. Of note, the results of the TIME trial are in contrast with those of a recent meta-analysis, suggesting that adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters.\textsuperscript{9} Large controlled randomized trials with clinical endpoints, like the ongoing BAMI trial funded by the European Community, are strongly warranted in order to provide convincing answers in this controversial area.

### Antiplatelet therapy

Antiplatelet therapy is an essential component in the treatment of ACS. Several still open questions were addressed by recent studies. The ACCOAST trial, carried out in 4033 patients with non-ST-elevation ACS and elevated Tn levels, compared prasugrel given at the time of diagnosis (30 mg prior angiography and 30 mg prior PCI) with its administration after coronary angiography followed by PCI (60 mg).\textsuperscript{10} The pre-treatment strategy did not reduce the risk of death from cardiovascular causes, MI, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy through Day 7, but it resulted in the increased risk of bleeding. The rates of thrombolyis in myocardial infarction major bleeding and life-threatening
bleeding not related to coronary artery bypass grafting were increased by Factors 3 and 6, respectively. Accordingly, the recommendation of the European Society of Cardiology guidelines that prasugrel is only indicated for planned PCI remains unchanged. It remains open whether this also applies to clopidogrel and ticagrelor.

The long-term benefit of potent antiplatelet treatment in patients with ACS and angiographically documented coronary artery disease was investigated in a pre-specified sub-analysis of the TRILOGY trial. In contrast to the total trial cohort, fewer cardiovascular deaths, AMI, or strokes over 30-month follow-up were observed among patients who had angiography and were on prasugrel when compared with those who were on clopidogrel. Bleeding complications were rare and risk tended to be higher with prasugrel, but it did not differ significantly between treatment groups over this long follow-up period. Perhaps, a sizeable proportion of patients are falsely classified as ACS when coronary artery disease is not documented by imaging, thus diluting the potential benefit of potent antiplatelet therapy.

Another clinical challenge relates to cessation of dual antiplatelet therapy (DAPT) after PCI. The risk of DAPT cessation was systematically analysed in the PARIS registry based on 5018 patients (ACS representing ~40% of cases). Of note, most events (74%) occurred while patients were on DAPT rather than after its cessation. Interruption (for instance for surgery) or disruption (for instance for bleeding) increased the risk of events predominantly in the first 7 days (seven-fold increase) or between 8 and 30 days (two-fold increase). In contrast, planned discontinuation as recommended by the physicians and continuation of DAPT was associated with a 37% lower risk of events.

Oral P2Y₁₂ inhibitors have been shown to reduce the risk of ischaemic events after ACS and PCI, but a delayed onset of action related to absorption and metabolic transformations may limit their efficacy. Recently, cangrelor, a novel intravenous antiplatelet agent characterized by fast-onset, potent and reversible P2Y₁₂ inhibition, and short half-life of 3–6 min, was investigated in >25 000 patients in three large trials, the latest being PHOENIX CHAMPION. Almost half of the 11 145 patients included in this trial had ACS and were randomized to clopidogrel or cangrelor before PCI. Cangrelor significantly reduced the rate of ischaemic events (including stent thrombosis) by 22% at 48 h with no significant increase in severe bleeding. This was confirmed in a meta-analysis which included the two other cangrelor trials. Cangrelor reduced a pre-specified primary efficacy composite endpoint of death, AMI, ischaemia-driven revascularization, or stent thrombosis at 48 h by 22% (3.8% for cangrelor vs. 4.7% for control) and stent thrombosis alone by 41% (0.5 vs. 0.8%). No difference was observed in the rate of GUSTO moderate bleeding (0.6 vs. 0.4%), or of transfusions (0.7 vs. 0.6%), while cangrelor increased the rate of GUSTO mild bleeding (16.8 vs. 13.0%, P < 0.0001). Therefore, cangrelor seems to be an interesting option for bridging until oral P2Y₁₂ inhibitors are effective or as an alternative when glycoprotein IIb/IIIa antagonists are associated with an increased risk of bleeding.

**Anticoagulation**

The role of adequate anticoagulation, particularly in the frame of PCI, remains an unresolved issue. Currently, unfractionated heparin or low-molecular-weight heparins are the most widely used agents in Europe, although guidelines recommend the direct thrombin inhibitor bivalirudin in an invasive and the factor Xa inhibitor fondaparinux in a conservative strategy. There have been rather conflicting results with different new oral anticoagulants. According to a meta-analysis of all studies, the addition of a new oral anticoagulant to DAPT results only in a modest reduction in cardiovascular

**Figure 2** Primary composite outcome (death and major bleeding) in the EUROMAX trial (reprinted with kind permission from ref.21).
events [hazard ratio (HR): 0.87; 0.80–0.95], but in a substantial increase in bleeding risk (HR: 2.34; 2.06–2.66). However, the results vary among trials, partly probably related to a very small therapeutic window. Indeed, while the APPRAISE-2 trial with apixaban failed to show a benefit, in contrast to the ATLAS-2 trial with rivaroxaban. Fewer studies have been carried out during the acute phase of coronary instability. Otamixaban, an intravenous factor Xa inhibitor with fast-onset and offset of action, was investigated in the large randomized TAO trial vs. the standard treatment with unfractionated heparin in combination with the glycoprotein llb/lll inhibitor epifibatide. In contrast to the positive signal from the Phase II trial SEPIA ACS, otamixaban did not reduce adverse events, while it doubled the bleeding rate.

There are lessons to learn from these trials regarding the management of patients undergoing PCI for ACS. It would appear that, in the acute phase of ACS, anticoagulation is less efficient than potent platelet inhibition, thus resulting in an unfavourable risk–benefit ratio, while the latter might become more favourable after the acute phase of coronary instability, although with a narrow therapeutic window.

Pre-hospital STEMI treatment

Pre-hospital fibrinolysis with timely coronary angiography in patients with early (<3 h) STEMI who could not undergo primary PCI within 1 h of the first medical contact was investigated in the STREAM study. The rate of the composite endpoint of death, shock, congestive heart failure, or re-infarction up to 30 days was similar to that observed after primary PCI, with a slightly increased risk of intracranial bleeding. Therefore, even under optimal conditions, fibrinolysis remains a second choice as long as PCI is available.

Anticoagulation in the pre-hospital setting in patients with STEMI has for the first time addressed in the EUROMAX trial comparing heparin and optional glycoprotein llb/lll with the thrombin inhibitor bivalirudin, which was previously shown to reduce mortality in the HORIZONS-AMI trial. In 2218 patients with STEMI, bivalirudin, started during transport for primary PCI, improved 30-day clinical outcomes with a reduction in major bleeding across all subgroups (2.6 vs. 6.0%; relative risk, 0.43; P < 0.001) (Figure 2), but with an increase in acute stent thrombosis (1.1 vs. 0.2%; relative risk, 6.11; 95% CI 1.37–27.24; P = 0.007). There was no difference in death and re-infarction (Figure 2). The impact on long-term hard endpoint outcomes needs to be awaited.

Conflict of interest: C.W.H. serves on advisory boards for AstraZeneca, Bayer, and Boehringer Ingelheim and received speaker honoraria from AstraZeneca, Bayer, Daiichi Sankyo, Pfizer, Lilly, SanofiAventis, and The Medicines Company. F.C. has nothing to report.

References


