The Year in Cardiology

The Year in Cardiology 2012: acute coronary syndromes

Nick E.J. West*

Department of Interventional Cardiology, Papworth Hospital, Cambridge CB23 3RE, UK

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This paper was edited by Filippo Crea, Dipartimento di Scienze Cardiovascolari, Universita Cattolica Rome, Rome, Italy

Patients presenting with acute coronary syndromes (ACS) remain amongst the highest-risk of all acute medical admissions. Despite significant reductions in morbidity and mortality via refinements in treatment methods in recent years, such individuals remain at a high risk of recurrent ischaemic events and death. Whilst 2012 has brought a wealth of novel data in the field of ACS regarding diagnosis and both medical and invasive management strategies, continued focus on this high-risk patient subset is necessary to further our understanding and improve patient outcomes.

Keywords
Acute coronary syndromes • Antiplatelet therapies • PPCI • STEMI • NSTEMI • Guidelines • ECG • Stem cell therapy • Coronary intervention • PCI • Microvascular obstruction

Introduction

There have been few recent years where the management of acute coronary syndromes (ACS) has not been significantly advanced in terms of novel therapies and treatment strategies. In the last 12 months, new societal guidance has been published from Europe and North America, and there have also been important ACS studies concerning non-invasive diagnostics, stent type/choice, and adjunctive therapies designed to reduce infarct size in percutaneous coronary intervention (PCI) for ACS. In similar fashion to recent years, the area most published in and most likely to alter practice concerns the choice and utilization of antiplatelet/anticoagulant strategies for ACS patients managed either medically or with an invasive/interventional strategy. This review will seek to summarize the most important advances in these areas over the last year.

Guideline updates

The ESC not only produced updated guidance on management of STEMI1 in 2012, but also produced a third version of the Universal Definition of Myocardial Infarction.2 The former document updates previous guidance from the ESC and contains important new recommendations in key areas (Table 1): the importance of early diagnosis is stressed, with first ECG in patients with suspected STEMI recommended within 10 min of first medical contact (FMC) and primary percutaneous coronary intervention (PPCI) for STEMI ideally within 90 min (rated ‘acceptable’ out to a maximum of 120 min). Such strict criteria may have an impact on more rural geographies where transit time to PPCI centres is an issue, and with this in mind, the guidance highlights the importance of collaborative networks to facilitate achievement of such targets. The guideline also emphasizes the importance of prompt assessment and management of atypical presentations not always considered under the umbrella of STEMI, including left bundle branch block (LBBB), paced rhythms, and isolated ST-segment elevation in lead aVR, especially when accompanied by symptoms consistent with myocardial ischaemia. Therapeutic hypothermia is now recommended for all resuscitated patients with STEMI complicated by cardiac arrest cases, with immediate coronary angiography with a view to follow-on PPCI when the ECG demonstrates persistent ST-segment elevation. Additionally, in the light of recently published studies and meta-analyses, including that of Kalesan et al.,3 drug-eluting stents (DES) are now routinely preferred to bare metal stents (BMS) in view of the reduced need for repeat revascularization and the lack of previously perceived hazard for stent thrombosis. The more potent antiplatelet agents prasugrel
and ticagrelor are also preferred to clopidogrel for all STEMI cases, with duration of dual antiplatelet therapy (DAPT) ideally for 1 year, but reduced to a strict minimum of 6 months for patients receiving DES.

Accompanying and integral to such guidance was the Third Universal Definition of Myocardial Infarction,\(^1\) published simultaneously with the STEMI guidance. This guideline endorses cardiac troponin as the biomarker of choice to detect myocardial necrosis, with spontaneously occurring myocardial infarction (MI) defined as an elevation above the 99th percentile upper reference value for the specific assay used. There is further development and clarification of MI in different settings to allow standardization across trials and registries, in particular after revascularization procedures: after CABG with normal baseline troponin, MI is defined as a rise to a 29% increase in mortality at 1 year and 24% at 5 years. These findings have important implications for the optimization of patient therapies after MI (including the use of rate-limiting agents such as beta-blockers, calcium channel-blockers, and ivabradine), although large randomized trials are needed to confirm that interventions to reduce heart rate will replicate the benefits observed in this study.

Two important studies concerning the use of coronary computed tomographic angiography as a triage tool for suspected ACS were published this year;\(^8,9\) the findings are discussed fully in another review in this series, but in essence, while improving the efficiency of the emergency department, the studies suggest no cost improvement and an additional hazard for radiation exposure without clear clinical outcome benefit, suggesting that such a strategy has little data to support it at the present time.

### Risk stratification
Identification and appropriate triage of patients presenting to emergency departments with acute chest pain remains a difficult dilemma: many are low-risk and have a non-cardiac origin, but a significant minority with coronary artery disease may not be picked up on clinical grounds even when accompanied by appropriate tests, including ECG and biomarker estimation used in conjunction with a clinical risk score (e.g. GRACE, TIMI). As endorsed in ESC guidance,\(^1\) there has been increasing interest in non-typical ECG patterns for the diagnosis of STEMI; although LBBB is an accepted surrogate, Widimsky et al.\(^5\) retrospectively analysed 6742 patients admitted to hospital with acute MI and found that in patients presenting with right bundle branch block, a blocked epicardial vessel was more common (51.7% vs. 39.4%; \(P < 0.001\)) and incidence of both shock and mortality comparable with LBBB (14.3% vs. 13.1%; \(P = NS\); and 15.8% vs. 15.4%; \(P = NS\), respectively). In a similar vein, Wong et al.\(^6\) demonstrated the importance of ST-elevation in lead aVR, often viewed as indicative of left main stem occlusion, betokening increased mortality in patients presenting with both inferior and anterior infarction.

Perhaps the most important data regarding the ECG in 2012 were also the most simple: Antoni et al.\(^7\) highlighted a powerful and very simple method of risk stratification: they found that heart rate measured on a 12-lead ECG at discharge after PPCI is a strong and independent predictor of mortality at 1 and 4 years of follow-up (Figure 1). Patients with a discharge heart rate of \(\geq 70\) b.p.m. had a two-fold higher mortality at both follow-up time points, with every increase of 5 b.p.m. in heart rate equating to a 29% increase in mortality at 1 year and 24% at 5 years. These findings have important implications for the optimization of patient therapies after MI (including the use of rate-limiting agents such as beta-blockers, calcium channel-blockers, and ivabradine), although large randomized trials are needed to confirm that interventions to reduce heart rate will replicate the benefits observed in this study.

### Antiplatelet and anticoagulant therapies
As in preceding years, the major area of interest in ACS and ACS PCI in 2012 has been the further refinement of optimal antiplatelet/anticoagulant regimens; as mortality and adverse event rates fall year-on-year for ACS patients whether they are managed medically or invasively, the focus on the balance between prevention of ischaemic events and avoidance of bleeding sharpens ever more. One agent potentially fulfilling some of these requirements is the factor Xa inhibitor rivaroxaban; in the previous ATLAS ACS-TIMI 46 phase 2 study, patients with a recent ACS receiving

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**Table 1** Summary of new changes in ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation\(^1\)

<table>
<thead>
<tr>
<th>Field</th>
<th>New changes</th>
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</thead>
<tbody>
<tr>
<td>Early diagnosis</td>
<td>First ECG within 10 min of FMC</td>
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<td></td>
<td>Attention to atypical presentations (e.g. LBBB, paced rhythm, ST elevation in aVR)</td>
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<tr>
<td>Cardiac arrest</td>
<td>Therapeutic hypothermia after successful resuscitation</td>
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<td></td>
<td>Immediate angiography and follow-on PCI for resuscitated STEMI</td>
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<td>Logistics</td>
<td>Regional networks to deliver timely PCI</td>
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<td></td>
<td>All PCI centres to be 24/7-capable</td>
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<td></td>
<td>New time standards for FMC to PCI (maximum (\leq 120) mins)</td>
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<tr>
<td>Procedural issues</td>
<td>DES now preferred to BMS</td>
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<tr>
<td></td>
<td>Ticagrelor or prasugrel preferred to clopidogrel</td>
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<tr>
<td></td>
<td>DAPT to continue to 12 months ideally—minimum 1 month for BMS, 6 months for DES</td>
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<tr>
<td>Post-procedure</td>
<td>Hospital discharge after 72 h post-PPCI for low-risk patients</td>
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<td></td>
<td>Mandatory assessment of LV function after acute phase</td>
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<td></td>
<td>Assessment of ischaemia for patients with residual untreated multivessel disease</td>
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</tbody>
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Rivaroxaban had improved outcomes with a dose-dependent increase in bleeding compared with placebo when used in addition to standard therapies. The ATLAS ACS 2-TIMI 51 study therefore randomized 15,526 patients with a recent ACS to receive low doses of 2.5 or 5 mg rivaroxaban twice daily or placebo. The previous positive findings were reproduced with a reduction in the composite endpoint of cardiovascular death, MI, or stroke (HR 0.84; 95% CI 0.74–0.96; \( P = 0.008 \)). However, there was more non-fatal bleeding with rivaroxaban overall, particularly at the higher dose. The 2.5 mg twice-daily dose had fewer fatal bleeding events than the 5 mg twice-daily regimen (0.1 vs. 0.4%; \( P = 0.04 \)) and resulted in lower cardiovascular and all-cause mortality (2.7 vs. 4.1%; \( P = 0.002 \) and 2.9 vs. 4.5%; \( P = 0.002 \), respectively). It would therefore appear that rivaroxaban may be a useful adjunct to currently available therapies, especially when targeted at patients with low potential for bleeding.

Previous studies have demonstrated that platelet inhibition can be improved by either increasing dose or switching to more potent antiplatelet agents, but whether this results in improved clinical outcomes remains to be seen. The TRIGGER-PCI study\(^ {11} \) (presented in 2011 but published in 2012) aimed to investigate whether switching patients with residual high platelet reactivity on clopidogrel after elective PCI with DES to prasugrel would improve outcomes; the study was stopped early owing to a low incidence of the primary endpoint (death/MI at 6 months) with no difference between clopidogrel- and prasugrel-treated groups (total of 1 single event) despite increased platelet inhibition. The larger scale TRILOGY-ACS study\(^ {12} \) randomized 7243 patients with unstable angina or NSTEMI not undergoing revascularization to prasugrel or clopidogrel. There was no difference between the groups in terms of the primary endpoint (cardiovascular death/MI/stroke) and no change in bleeding events either. These two studies underscore the fact that current DAPT regimens are both efficacious and safe; that said, some patients clearly are at risk of either recurrent ischaemic events and/or bleeding, and perhaps the way forward should be to attempt to seek alternative triage methods to identify the individuals at highest risk of further events and alter therapies accordingly.

In terms of pharmacology delivered in the catheterization laboratory/PCI setting, the direct thrombin inhibitor bivalirudin has already shown promise in reducing bleeding events without sacrificing anti-ischaemic efficacy in PPCI for STEMI, resulting in widespread endorsement in societal guidance. A pooled analysis of the ACUITY and ISAR-REACT 4 studies\(^ {13} \) examined 3798 NSTEMI cases undergoing PCI randomized to receive either bivalirudin or heparin plus a glycoprotein IIb/IIIa inhibitor (GPI). The
Coronary intervention and cardioprotection in acute coronary syndromes

Microvascular obstruction during PCI for ACS/STEMI is associated with increased infarct size and adverse prognosis; its pathophysiology is thought to be a combination of mechanical distal embolization of thrombus and plaque constituents during PCI coupled with enhanced constriction/hyperreactivity of the distal vascular bed. Three studies in 2012 in the setting of PPCI for STEMI have therefore sought to reduce distal embolization: in the INFUSE-AMI trial, 1452 patients presenting within the first 4 h of an anterior STEMI were randomized in a 2 × 2 factorial design to receive either manual aspiration thrombectomy or no thrombectomy and intracoronary bolus abciximab delivered via the ClearWay catheter (Atrium Medical, Hudson, NH, USA) or no abciximab; all patients received bivalirudin as standard therapy. Manual thrombectomy did not affect infarct size assessed by cardiac magnetic resonance imaging (MRI) at 30 days, but bolus intracoronary abciximab did [median infarct mass 18.7 g (IQR 7.4–31.3 g) vs. 24.0 g (IQR 12.1–34.2 g); P = 0.03]. Although these are encouraging findings, the lack of a comparator with conventionally delivered intravenous abciximab is a potential concern, especially given the negative findings of the much larger AIDA-STEMI study (n = 2065) that examined intracoronary vs. intravenous abciximab. Just as the overall study failed to show any improvement in hard clinical endpoints, the AIDA-STEMI MRI substudy (n = 795) failed to show any improvement in infarct size or reperfusion injury. The third and perhaps most novel strategy to reduce infarct size was the use of a BMS covered on its outer surface with a mesh micronet designed to trap and hold potentially friable material that might embolize distally at the time of PCI. The MASTER study randomized 433 STEMI patients to PPCI with conventional BMS or DES at the operator’s discretion vs. the novel MGuard stent (InspireMD, Tel Aviv, Israel); the primary endpoint of complete ST-segment resolution was significantly better in patients receiving MGuard (57.85 vs. 44.7%; P = 0.008), as was the achievement of TIMI grade 3 flow in the treated vessel (91.7 vs. 82.9%; P = 0.006); however, median ST-segment resolution did not differ between treatment groups, myocardial blush grade was no different, and safety outcomes at 30 days (death, adverse events) as well as overall MRI-determined infarct mass were also similar. Clearly, longer term data in a numerically larger cohort will be required to confirm these findings before wider uptake of this technology, especially given the potential for higher TVR rates that may accrue with a BMS platform when compared with current-generation DES (as now endorsed for PPCI in ESC guidance).

Although most attempts to reduce infarct size/increase myocardial salvage during STEMI have focused on pharmacological or PCI-based changes in techniques such as those listed earlier, other mechanisms have been investigated but these have similarly failed to show evidence of substantial improvements in outcome, perhaps indicating that PCI safety and efficacy are approaching their zenith. Like ischaemic pre-conditioning, post-conditioning (further episodes of repeated reversible ischaemia during early reperfusion) remains an area of interest, and has been shown to reduce infarct size by enzymatic criteria, although MRI-based studies are conflicting. A meta-analysis by Zhou et al. 18 seemed...
to indicate that, when considering 10 small randomized controlled studies of post-conditioning, there was an overall benefit with such a strategy. The POST study\(^2^9\) included 700 patients, randomized to receive four cycles of 1 min balloon occlusion/1 min deflation within 1 min of restoration of coronary flow during PPCI vs. standard therapy. Disappointingly, given the large size and statistical power of this study, the primary endpoint of complete ST-segment resolution was not achieved, and the numbers were too small to make definitive comments on clinical outcomes, which were nevertheless similar at 30 days.

In fact, comparing the four studies reviewed earlier in cardioprotection, there remains little to choose between strategies as evidenced by the relatively minor differences between surrogate endpoints employed regardless of therapeutic intervention chosen (Figure 2).

Cell therapies in AMI

As an alternative to protecting the myocardium against damage either in the setting of MI or during PCI, there has been increasing interest in regenerative methods aimed at repairing the myocardium with cell-based therapies. Although stem cell therapies have held much promise, the two studies related to ACS presented in the dedicated late-breaking trials session at the AHA were disappointing. The Swiss-AMI study\(^2^0\) randomized 200 STEMI patients after PPCI to placebo, early (5–7 days) or late (3–4 weeks) intracoronary infusion of autologous bone marrow–derived mononuclear cells (BMCs). Neither infusion approach affected the primary endpoint, LVEF, nor the secondary endpoints of LV nuclear cells (BMCs). Neither infusion approach affected the point where even in the highest risk patients such as those presenting with ACS, small improvements may be difficult to discern despite large well-designed - and -conducted studies.

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References


