

# ALMANAC 2011: ACUTE CORONARY SYNDROMES

## THE NATIONAL SOCIETY JOURNALS PRESENT SELECTED RESEARCH THAT HAS DRIVEN RECENT ADVANCES IN CLINICAL CARDIOLOGY

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### Summary

This overview highlights some recent advances in the epidemiology, diagnosis, risk stratification and treatment of acute coronary syndromes. The sheer volume of new studies reflects the robust state of global cardiovascular research but the focus here is on findings that are of most interest to the practising cardiologist.

Incidence and mortality rates for myocardial infarction are in decline, probably owing to a combination of lifestyle changes, particularly smoking cessation, and improved pharmacological and interventional treatment. Troponins remain central for diagnosis and new high-sensitivity assays are further lowering detection thresholds and improving outcomes. The incremental diagnostic value of other circulating biomarkers remains unclear and for risk stratification simple clinical algorithms such as the GRACE score have proved more useful.

Primary PCI with minimal treatment delay is the most effective reperfusion strategy in ST elevation myocardial infarction (STEMI). Radial access is associated with less bleeding than with the femoral approach, but outcomes appear similar.

Manual thrombectomy limits distal embolisation and infarct size while drug-eluting stents reduce the need for further revascularisation procedures. Non-culprit disease is best dealt with electively as a staged procedure after primary PCI has been completed. The development of antithrombotic and antiplatelet regimens for primary PCI continues to evolve, with new indications for fondaparinux and bivalirudin as well as small-molecule glycoprotein (GP) IIb/IIIa inhibitors. If timely primary PCI is unavailable, fibrinolytic treatment remains an option but a strategy of early angiographic assessment is recommended for all patients.

Non-ST segment elevation myocardial infarction (NSTEMI) is now the dominant phenotype and outcomes after the acute phase are significantly worse than for STEMI. Many patients with NSTEMI remain undertreated and there is a large body of recent work seeking to define the most effective antithrombotic and antiplatelet regimens for this group of patients. The benefits of early invasive treatment for most patients are not in dispute but optimal timing remains unresolved.

Cardiac rehabilitation is recommended for all patients with acute myocardial infarction but take-up rates are disappointing. Home-based programmes are effective and may be more acceptable for many patients. Evidence for the benefits of lifestyle modification and pharmacotherapy for secondary prevention continues to accumulate but the argument for omega-3 fatty acid supplements is now hard to sustain

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Competing interests: None  
Provenance and peer review: Commissioned; internally peer reviewed.

following recent negative trials. Implantable cardioverter-defibrillators for patients with severe myocardial infarction protect against sudden death but for primary prevention should be based on left ventricular ejection fraction measurements late (around 40 days) after presentation, earlier deployment showing no mortality benefit.

## Incidence and mode of presentation

Temporal trends for the global coronary epidemic vary by region but in most developed countries mortality is in decline.<sup>1</sup> Lifestyle adjustments have contributed to this decline—most recently, the implementation of comprehensive smoke-free legislation in many countries that has already caused significant reductions in acute coronary events.<sup>2</sup> Smoking, a potent thrombogenic stimulus, is a major determinant of STEMI<sup>3</sup> and a recent analysis from Kaiser Permanente in California - where smoke-free legislation is strictly enforced—showed a 62% decline in STEMI between 1999 and 2008 while NSTEMI increased by 30%.<sup>4</sup> Overall, there was a 24% reduction in hospitalisations for acute coronary syndromes despite lowering of diagnostic thresholds by sensitive troponin biomarkers.<sup>5</sup> This was accompanied by improvement in the age- and sex- adjusted 30-day mortality from 10.5% in 1999 to 7.8% in 2008. Increasing rates of interventional management no doubt contributed to the improved outcomes but parallel increases in plaque-stabilising treatment with high-dose statins must also have played a role<sup>6</sup> because vulnerable thin-cap fibroatheromas, often remote from the infarct-related artery and unrelated to stenosis severity, are the sites at which recurrent plaque events usually occur.<sup>7,8</sup>

## Diagnosis

Diagnostic definitions of acute coronary syndromes are internationally agreed based on troponin release and symptomatic, electrocardiographic, or functional criteria.<sup>9</sup>

## Troponins

Demonstration of a changing troponin concentration in the first 24 h with at least one value above the decision limit is central to the diagnosis of acute myocardial infarction. Now available are high-sensitivity troponin assays permitting significant reductions in the threshold for detection. An early study evaluated four high-sensitivity assays in 718 patients with suspected acute coronary syndrome, 17% of whom had acute myocardial infarction. Diagnostic performance was excellent, the area under the receiver operator curves ranging from 0.95 to 0.96 compared with 0.90 for the standard assay.<sup>10</sup> The implications for cardiac outcomes and clinical management were assessed in a more recent study in which high-sensitivity troponin I was measured in 1038 patients with suspected acute coronary syndrome.<sup>11</sup> Values below the previous limit of detection (0.20 ng/ml)—conventionally considered 'normal'—showed graded association with death or non-fatal myocardial infarction, with rates of 7% and 39% for troponin concentrations of <0.05 ng/ml and 0.05–0.19 ng/ml, respectively. When the investigators lowered the diagnostic threshold to 0.05 ng/ml in a further 1054 patients, communicating troponin values to clinicians, the risk of death and recurrent myocardial infarction in patients with troponin concentrations 0.05–0.19 ng/ml was reduced from 39% to 12%. The investigators concluded that lowering the diagnostic threshold by clinical application of high-sensitivity troponin assay has the potential to identify many high-risk individuals with suspected acute coronary syndrome and produce major improvements in their prognosis.

## Other diagnostic biomarkers

Studies evaluating new biomarkers for the early diagnosis of myocardial infarction have been the subject of a recent systematic review.<sup>12</sup> The quality of these studies has often been poor with only 16% providing any information about incremental value compared with other diagnostic data. Myoglobin, for example, appears to be useful to rule out myocardial infarction in the first 6 h but evidence that it adds value to clinical symptoms, ECG and troponin testing is

limited. Of the new diagnostic biomarkers, ischaemia-modified albumin and heart-type fatty acid-binding protein (H-FABP) showed initial promise, but already a meta-analysis has concluded that H-FABP does not fulfil the requirements needed for early diagnosis when used as a stand-alone test and called for evidence that it adds to clinical evaluation and other diagnostic tests.<sup>13</sup>

### Point-of-care diagnosis with a panel of biomarkers

Whether biomarker panels have a specific role for early diagnosis of myocardial infarction in the emergency room has been evaluated in two recent studies, both using a point-of-care panel of troponin I, creatine kinase-MB (CK-MB) and myoglobin. RATPAC recruited 2243 patients with suspected myocardial infarction and randomised them to standard care or panel evaluation on admission to the emergency room and 90 min later.<sup>14</sup> Point-of-care panel evaluation was associated with a 32% rate of 'successful' (no re-attendance with major coronary events) discharge from the emergency room, compared with 13% for standard care; hospital bed use was unaffected. However, a substudy to examine the diagnostic efficiency of the individual cardiac markers and their accuracy for the final diagnosis of acute myocardial infarction showed that point-of-care myoglobin and CK-MB did not provide further diagnostic information over that provided by troponin I for early diagnosis or exclusion of myocardial infarction.<sup>15</sup> ASPECT was an observational study of 3582 patients in which an accelerated diagnostic panel (ADP) of TIMI score, coupled with the point-of-care panel of biomarkers and ECG findings, identified 352 as low risk.<sup>16</sup> Only three of these patients went on to experience a major adverse cardiac event, making the ADP a highly sensitive rule-out for myocardial infarction in low-risk patients, as reflected by a negative predictive value of 99.1%. However, there was no control group in ASPECT, nor an analysis of the incremental value offered by individual components of the biomarker panel. Based on the RATPAC subgroup analysis, therefore, it seems clear that troponin remains the most useful biomarker for diagnosis of myocar-

dial infarction in the emergency room and current evidence is insufficient to advocate biomarker panels for this purpose.

### Electrocardiogram

Guideline recommendations are for urgent reperfusion therapy according to STEMI pathways in patients with suspected myocardial infarction presenting with left bundle branch block (LBBB). However, a retrospective analysis of 892 patients in a Mayo Clinic STEMI registry, found that of the 36 who presented with new LBBB, only 12 (33%) had a final diagnosis of acute myocardial infarction.<sup>17</sup> These data show that LBBB is of limited diagnostic utility in suspected myocardial infarction and provide a case for new diagnostic strategies in this high-risk group. Also at high risk are patients with acute myocardial infarction caused by proximal left anterior descending coronary artery (LAD) occlusion. A report that this may be associated with a distinct ECG pattern has now been confirmed in a series of 35 patients who underwent primary PCI of the LAD, all of whom showed ST-segment depression at the J-point with up-sloping ST segments and tall, symmetrical T-waves in the precordial leads of the 12-lead ECG.<sup>18,19</sup> The authors recommend that this ECG pattern in patients presenting with suspected myocardial infarction should prompt triage for immediate reperfusion therapy.

### Imaging

Echocardiography provides the most readily available imaging modality for acute phase diagnosis of myocardial infarction by identifying new left ventricular regional wall motion abnormality. A new diagnostic application for identifying those patients with NSTEMI who have complete coronary occlusions was recently described.<sup>20</sup> In such patients, circumferential strain measured within 1 h of admission was independently diagnostic, values  $\geq -10\%$  showing 90% sensitivity and 88% specificity for angiographic coronary occlusion. The authors suggest that strain measurements in the acute phase of NSTEMI might be used for triaging patients for immediate reperfusion therapy.

## Risk stratification

The risk of death and other ischaemic events in patients with acute coronary syndromes varies considerably across diagnostic phenotypes. Objective criteria to quantify risk are now increasingly used to guide treatment and determine prognosis.

### Clinical factors

Clinical factors are used intuitively by clinicians. They recognise that risk increases with age and shows important gender differences—young women with STEMI, for example, having a 15–20% higher mortality risk than men.<sup>21</sup> ECG criteria<sup>22</sup> and routine biochemistry are also used for risk stratification, outcomes worsening with admission hyperglycaemia and also it seems with admission hypoglycaemia.<sup>23,24</sup> Despite clinicians' reliance on clinical assessments of risk it is now clear that they often get it wrong and a recent study has shown little association with objective measures of risk using validated risk scores.<sup>25</sup>

### Diagnostic biomarkers

Increasing troponin release in NSTEMI is associated with a proportionate increase in the risk of lethal arrhythmias, cardiogenic shock, new heart failure and death.<sup>26</sup> C-reactive protein, the most widely studied prognostic biomarker, is also moderately predictive of adverse outcomes in acute coronary syndromes, a recent meta-analysis reporting a pooled RR of 2.18 (1.77 to 2.68) for the top (>10 mg/l) compared with the bottom (≤3 mg/l) category of values.<sup>27</sup> Generally speaking, however, individual biomarkers have yet to find a useful clinical role—a recent 5-year follow-up of patients with NSTEMI included in FRISC II reporting that none of N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein, cardiac troponin I and estimated glomerular filtration rate provided incremental prognostic value to established risk indicators, except NT-proBNP for 6-week outcomes.<sup>28</sup> Combining multiple biomarkers may improve predictive power for adverse outcomes but confirmation of incremental value over established risk scores is still awaited.<sup>29</sup>

## Risk scores

Validated risk scores based on a range of readily available factors provide the most effective means of risk stratifying patients with acute coronary syndromes. The GRACE score is widely used and in a comparative validation study involving 100 686 cases of acute coronary syndromes its discriminative performance in predicting mortality compared favourably with a range of other risk models including PURSUIT, GUSTO-1, GRACE, SRI and EMMACE.<sup>30</sup> The GRACE score appears to have lost none of its clinical value with the availability of high-sensitivity cardiac troponin assays. In an international cohort of 370 patients with acute coronary syndromes, the area under the curve of the GRACE score was 0.87 and 0.88 for in-hospital and 1-year mortality, and addition of high-sensitivity cardiac troponin produced no improvement in the mortality prediction.<sup>31</sup>

## Primary percutaneous coronary intervention

The MINAP public report for England and Wales records that 70% of all patients with STEMI received reperfusion therapy in 2010/2011, of whom 81% received primary PCI.<sup>32</sup> The drive towards primary PCI, based on evidence of a sustained mortality benefit compared with fibrinolysis,<sup>33</sup> has been underpinned by the establishment of regional networks that have defined local standards of care and provided infrastructure for staffing heart attack centres.<sup>34,35</sup>

Timely treatment is essential to maximise prognostic benefit,<sup>36,37</sup> and important as it is to achieve door-to-balloon times within 90 min, other intrinsic delays within the healthcare process also need consideration. Thus, a Danish registry analysis of 6209 patients with STEMI found that 'system delay' (time from first contact with the healthcare system to the initiation of reperfusion therapy)—as well as door-to-balloon time—was a key modifiable risk factor, with an HR for mortality during the next 3.4 years of 1.22 (95% CI 1.15 to 1.29;  $p < 0.001$ ) per 1 h increase in system delay.<sup>38</sup> The findings emphasise the importance of minimising transfer times from non-PCI

hospitals and introducing policies of pre-hospital diagnosis to permit direct delivery of patients with STEMI to interventional centres. Also important are strategies to reduce the time it takes people with chest pain to call the emergency services. Women take significantly longer than men but, despite a US campaign to increase women's awareness of their risk of heart disease, a recent study found it had no effect on the gender gap or the time it took women to call the emergency services.<sup>39</sup>

### Vascular access

Primary PCI by radial rather than femoral access is the preferred approach for an increasing number of operators.<sup>40</sup> Its main advantage appears to be a lower rate of bleeding complications—the randomised RIVAL trial of radial versus femoral access in 7021 patients with acute coronary syndromes reporting a trend towards lower bleeding rates at 30 days (0.7% vs 0.9%), associated with significantly lower rates of access-site complications, including large haematomas and pseudoaneurysms.<sup>41</sup> Findings were similar in a recent observational study of 1051 primary PCI cases with vascular complication rates of 0% and 1.9% for radial versus femoral access.<sup>42</sup> However, RIVAL found no outcome advantage for radial access, and femoral access is still preferred by many operators<sup>43</sup> because access is more predictable and procedure times may be shorter than with the radial approach.<sup>44 45</sup>

### Stenting

Concerns about stent thrombosis led to recommendations for bare metal stents in primary PCI but randomised trials have now confirmed important advantages for drug-eluting stents. The HORIZONS-AMI 3-year results showed lower rates of target lesion revascularisation for the 2257 patients randomised to paclitaxel-eluting stents than for the 749 patients randomised to bare metal stents (9.4% vs 15.1%).<sup>46</sup> There was no difference by stent type in rates of death, reinfarction, stroke or stent thrombosis. Drug-eluting stents are, therefore, preferred in primary PCI but they commit the patient to a full 12 months of dual antiplatelet treatment and if urgent surgery is planned or

there is a high risk of bleeding for other reasons bare metal stents should be chosen.

### Culprit lesion versus multivessel PCI

The main purpose of primary PCI is to achieve reperfusion of jeopardised myocardium by reopening the culprit coronary artery. Whether it is safe or desirable to treat disease within non-culprit vessels during the primary PCI procedure or as a staged procedure afterwards has been the subject of recent investigation. A small randomised trial of 214 patients with multivessel disease found that adverse event rates during a mean follow-up of 2.5 years were higher with culprit PCI than with multivessel PCI whether performed during the primary PCI procedure or, better, as a staged procedure afterwards.<sup>47</sup> This trial has now been included in a meta-analysis of four prospective and 14 retrospective studies involving 40 280 patients, which came to a similar conclusion in showing that staged PCI was associated with lower mortality compared with culprit PCI.<sup>48</sup> However, multivessel PCI during the primary procedure was associated with the highest mortality. A post hoc analysis of the HORIZONS-AMI trial also found that staged PCI was associated with lower 1-year mortality compared with culprit PCI (2.3% vs 9.2%).<sup>49</sup> These data, are consistent in showing that multivessel disease is best dealt with electively as a staged procedure after the primary PCI procedure has been completed.

### Thrombectomy

Thrombotic coronary occlusion is the pathological event triggering STEMI and provides the logic for adjunctive thrombectomy during primary PCI. A variety of devices have been developed for this purpose but the simplest, manual thrombus aspiration, has emerged as the best, with evidence of better reperfusion during the acute phase of STEMI translating into a survival advantage at 1 year compared with conventional primary PCI.<sup>50 51</sup> MRI has confirmed that thrombus aspiration reduces microvascular obstruction during primary PCI and limits infarct size at 3 months.<sup>52</sup> A more recent analysis of pooled individual

patient data from three randomised trials found that the trend for worsening myocardial reperfusion with time from admission to primary PCI was effectively abolished by thrombus aspiration, suggesting particular benefits in the event of procedural delay.<sup>53</sup> More complex thrombectomy devices are not recommended for use in STEMI. Thus assessments of infarct size reduction in two trials—JETSTENT comparing Angiojet rheolytic thrombectomy with primary direct stenting and PREPARE comparing simultaneous proximal embolic protection and manual thrombus aspiration with manual thrombus aspiration—showed no significant benefit of these device strategies.<sup>54</sup> Consistent with this is a meta-analysis of thrombectomy trials showing that the mortality benefit for patients randomised to thrombus extraction is confined to patients treated with manual thrombectomy.<sup>56</sup>

### Antiplatelet strategies

Current recommendations are for loading doses of aspirin and clopidogrel immediately before primary PCI followed by maintenance treatment. Adjunctive treatment with GPIIb/IIIa receptor blockers provides more intensive platelet inhibition in the acute phase. The main purpose of treatment is to enhance thrombus resolution and to prevent recurrent thrombotic events, particularly stent thrombosis in the 9–12 months it takes for drug-eluting struts to endothelialise (1–3 months for bare metal struts). Newer, drugs that block the ADP P2Y<sub>12</sub> receptor more potently than clopidogrel are now available<sup>57</sup> and have been evaluated in combination with aspirin in patients undergoing primary PCI. In the TRITON-TIMI 38 trial of dual antiplatelet treatment, prasugrel reduced the primary outcome of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke compared with clopidogrel (6.5% vs 9.5%), but this was associated with a significantly greater risk of major bleeding, including fatal bleeding, raising important safety concerns.<sup>58</sup> Ticagrelor has also been evaluated against clopidogrel in a substudy of the PLATO trial and like prasugrel it proved more effective in reducing the primary outcome of cardiovascular death, myocardial infarction or stroke, although the absolute

difference was small (9.0% vs 10.7%).<sup>59</sup> Strikingly, however, there appeared to be enhanced bleeding, and ticagrelor now has a guideline recommendation for use in primary PCI, although its final place in the therapeutic arsenal must await cost-effectiveness and long-term safety studies.

Abciximab, given intravenously, has been the most widely used GPIIb/IIIa receptor blocker in patients with STEMI undergoing primary PCI. Benefits appear to be inversely related to inflammatory burden<sup>60</sup> and may be enhanced by intracoronary administration, a recent meta-analysis reporting improved clinical outcomes by this route.<sup>61</sup> However, abciximab is expensive and there are now studies confirming non-inferiority of ‘small-molecule’ GPIIb/IIIa receptor blockers. Thus, investigators using the Swedish Coronary Angiography and Angioplasty Registry compared 2355 primary PCI patients who received eptifibatide with 9124 who received abciximab and found similar rates of death or myocardial infarction during 1-year follow-up (15.0% vs 15.7%).<sup>62</sup> In a smaller study, 427 patients randomised either to eptifibatide or abciximab showed comparable rates of complete ST-segment resolution 60 min after primary PCI (62.6% vs 56.3%) with no significant differences between cardiovascular outcomes.<sup>63</sup> In the On-TIME 2 trial, another small molecule compound, tirofiban, in combination with aspirin and clopidogrel, provided more effective platelet inhibition than aspirin and clopidogrel alone in patients undergoing primary PCI. The degree of platelet inhibition showed significant relationship with major adverse cardiac events, including stent thrombosis.<sup>64</sup> These findings have yet to penetrate international guidelines but many centres are now switching from abciximab to small-molecule compounds to reduce pharmacological costs.

### Other antithrombotic drugs

#### Fondaparinux

Intravenous heparin during primary PCI further enhances thrombus resolution during primary PCI but ongoing treatment with low molecular weight heparin has now given way to fondaparinux, a synthetic

factor Xa inhibitor. A recent individual patient-level combined analysis of 26 512 patients from the OASIS 5 and 6 trials who were randomised to fondaparinux 2.5 mg daily or a heparin-based strategy has resolved uncertainty about the clinical value of fondaparinux in patients undergoing primary PCI by showing a better net clinical composite of death, myocardial infarction, stroke, or major bleeding (10.8% vs 9.4%; HR=0.87; p=0.008) in the subset of 19 085 patients treated invasively.<sup>65</sup> A similar benefit was found in patients treated conservatively. Fondaparinux is now widely used in preference to heparin in acute coronary syndromes.

### Bivalirudin

Bivalirudin is a direct thrombin inhibitor that showed superiority to a combined regimen of heparin plus a GPIIb/IIIa inhibitor in HORIZONS-AMI, largely owing to a lower rate of major bleeding (4.9% vs 8.3%).<sup>66</sup> All-cause mortality at 30 days was also lower in the bivalirudin group, with persistent benefit after 3 years (5.9% vs 7.7%), assuring a guideline recommendation for bivalirudin in primary PCI.<sup>46</sup> It should be noted, however, that femoral artery access was used in 94.1% of the HORIZONS-AMI population and whether the reduction in bleeding with bivalirudin applies equally to centres where radial access is the preferred approach is not known.

### Fibrinolytic treatment

Evidence that fibrinolysis is less effective than primary PCI in the emergency management of STEMI, has now been reinforced by evidence of reduced cost-effectiveness,<sup>67</sup> yet a significant minority of patients in England and Wales continue to be treated with it.<sup>32</sup> This may be justified if fibrinolysis can be delivered within 30 min after presentation when primary PCI is not immediately available, because treatment delays by either modality are associated with substantial increases in mortality.<sup>36</sup> This has provided justification for programmes of pre-hospital thrombolysis, particularly in rural regions where transport times are prolonged, but enthusiasm for this approach may now be diminished by

evidence from the MINAP registry showing higher rates of reinfarction compared with in-hospital thrombolytic treatment for patients with STEMI.<sup>68</sup> The difference in reinfarction rates was only significant for tenecteplase (9.6% vs 6.4%), not reteplase, and was particularly marked when transport times exceeded 30 min. It was attributed to differences in the use of adjunctive antithrombotic treatment in the two treatment environments. Interestingly, bleeding complications were more common in the hospital environment where adjunctive antithrombotic treatment was more aggressive, consistent with recent data from RIKS-HIA showing that major bleeding complications among patients receiving fibrinolytic treatment continued to increase from 2001 to 2006 as antithrombotic treatments became more effective.<sup>69</sup> The availability of potent ADP P2Y<sub>12</sub> receptor blockers has raised further concerns about bleeding complications, and it was gratifying, therefore, that the PLATO trial substudy confirmed that event rates could be reduced with ticagrelor compared with clopidogrel without an increase in bleeding risk.<sup>70,71</sup>

The role of invasive treatment after fibrinolytic treatment in STEMI has been clarified in two recent meta-analyses of small and medium-size trials comparing strategies of routine early angiography for all patients with deferred or ischaemia-guided angiography.<sup>72,73</sup> Both meta-analyses reported that routine early angiography was associated with reductions in the rates of recurrent myocardial infarction and death and this strategy is now recommended in international guidelines.

### Non-ST-segment elevation myocardial infarction

NSTEMI has become the dominant mode of presentation for patients with acute myocardial infarction and in the recent analysis from Kaiser Permanente accounted for 66.9% of cases.<sup>4</sup> There has been a perception that NSTEMI is relatively benign despite evidence that prognosis after 2 months becomes substantially worse than with STEMI.<sup>21,74</sup> This may explain the tendency of doctors to under-treat NSTEMI based on a mismatch between perceived

and actual risk that distorts management decisions, perpetuating the 'treatment-risk paradox'.<sup>75</sup> Thus, despite a worse prognosis, patients with NSTEMI are less likely than patients with STEMI to receive optimal secondary prevention treatment.<sup>75</sup> Moreover, in a study of 13 489 NSTEMI admissions recorded in the MINAP registry, invasive management was associated with better outcomes but was applied inequitably, with lower rates in high-risk groups, including older patients, women and those with cardiac comorbidities.<sup>76</sup>

## Emergency management

Dual antiplatelet treatment with aspirin and clopidogrel is central to the management of NSTEMI.<sup>77</sup> The role of newer more potent ADP P2Y<sub>12</sub> receptor blockers remains undetermined, although ticagrelor looks promising, based on its ability to reduce ischaemic events compared with clopidogrel in NSTEMI as well as STEMI, without increasing the risk of bleeding.<sup>78</sup> Simultaneous treatment with fondaparinux is now recommended in preference to enoxaparin, based on the findings in OASIS 5 which compared these agents in 20 078 patients with acute coronary syndromes.<sup>79</sup> Patients randomised to fondaparinux showed a 50% reduction in major bleeding compared with enoxaparin, with no difference in the incidence of ischaemic events. The reduction in bleeding risk was comparable whether clopidogrel or GPIIb/IIIa receptor blockers were co-prescribed<sup>80</sup> and cost-effectiveness has now been confirmed.<sup>81</sup> Indications for bivalirudin in NSTEMI have been harder to define and although it has a licence for use in combination with aspirin and clopidogrel, this is based principally on its safety profile (lower bleeding risk), its efficacy for reducing ischaemic events being no greater than either heparin plus GPIIb/IIIa receptor blocker or bivalirudin plus GPIIb/IIIa receptor blockers.<sup>82</sup>

The majority of patients with NSTEMI benefit from interventional management,<sup>83</sup> but recent data suggest this could be delayed for at least 24 h unless continuing clinical instability unresponsive to GPIIb/IIIa receptor blockers calls for earlier action. Thus, in a randomised comparison of immediate versus deferred

PCI in 251 patients, the incidence at 30 days of the primary end point, a composite of death, non-fatal myocardial infarction or unplanned revascularisation, was significantly higher in the group receiving immediate PCI (60% vs 39%).<sup>84</sup> The difference persisted at 6 months' follow-up. Delaying intervention beyond 96 h is unlikely to be helpful, yet registry data show that this is common, particularly in high-risk patients who have most to gain from revascularisation.<sup>85</sup> The evidence for timely revascularisation is largely based on PCI data but a small proportion of patients require coronary artery bypass grafting (CABG). An analysis of US registry data showed that the timing of CABG has no palpable effect on outcomes, the composite of death, myocardial infarction, congestive heart failure, or cardiogenic shock being similar (12.6% vs 12.4%) whether CABG is done within 48 h of admission or later.<sup>86</sup> In general, therefore, early surgery is recommended to limit hospital stay and reduce resource use.

## Secondary prevention

### Cardiac rehabilitation

The benefit of cardiac rehabilitation among 30 161 Medicare beneficiaries, 20.5% of whom had recent myocardial infarction, was confirmed by a strong dose-response relationship between the number of rehabilitation sessions attended and long-term rates of death and myocardial infarction.<sup>87</sup> Yet a contemporary report of cardiac rehabilitation in the UK found that only 26% of eligible patients with myocardial infarction are recruited, with adherence rates of 65–85%.<sup>88</sup> Reasons for the poor uptake are complex but include the fact that many patients do not want to participate in centre-based group programmes. A systematic review has now reported that home-based programmes are equally effective in improving clinical and health-related quality-of-life outcomes and are more acceptable to many patients.<sup>89</sup> Healthcare costs are similar, supporting the further provision of home-based cardiac rehabilitation such as that described by investigators in Birmingham.<sup>90</sup> The recent demonstration of improved myocardial blood flow plus reductions in

circulating angiogenic cytokines in patients undergoing cardiac rehabilitation provides some reassurance that clinical improvement is physiologically based.<sup>91</sup>

### Lifestyle modification

An important component of cardiac rehabilitation is lifestyle adjustment to help protect against further coronary events. Top of the list is smoking cessation. A recent study of 1581 patients followed up for 13 years showed that the adjusted HR for all-cause mortality was lower by 43% in lifelong non-smokers and by 43% in patients who quit after myocardial infarction.<sup>92</sup> A new finding was that among persistent smokers, each reduction of five cigarettes smoked per day reduced the risk of death by 18%, providing some comfort for those patients for whom complete abstinence proves impossible. Even among patients who manage to quit, there remains the hazard of second-hand smoke exposure, as reflected by data from Scotland showing that adjusted all-cause and cardiovascular mortality among never-smoking survivors of myocardial infarction increases according to smoke exposure measured by serum cotinine concentration.<sup>93</sup> The message is clear that protection against recurrent events in survivors of myocardial infarction requires smoking cessation by the patient and also by those with whom the patient makes contact, particularly family members.

Together with smoking cessation, advice about exercise and diet delivered in formal programmes can have a salutary effect on modifiable risk profiles, including serum cholesterol, blood pressure and body mass index.<sup>94</sup> Dietary recommendations usually include  $\omega$ -3 fatty acid supplements<sup>95</sup> but this has now been questioned by the findings of two studies. In the first, 4837 patients with previous myocardial infarction were randomised to margarines containing marine n-3 fatty acids and plant-derived  $\alpha$ -linolenic acid in a 2x2 factorial design.<sup>96</sup> The rate of adverse cardiovascular events did not differ significantly among the study groups. In the second study, highly purified  $\omega$ -3 fatty acids were randomly allocated to 3851 patients with acute myocardial infarction followed up for 12 months.<sup>97</sup> There were no significant differences in rates of sudden

cardiac death (1.5% vs 1.5%), total mortality (4.6% vs 3.7%), or major adverse cerebrovascular and cardiovascular events (10.4% vs 8.8%) between treatment and placebo groups. The results of these two trials make recommendations for secondary prevention with  $\omega$ -3 fatty acid supplements after myocardial infarction difficult to sustain.

### Pharmacotherapy

The importance of optimal secondary prevention after myocardial infarction was emphasised in a modelling study, in which greater absolute gains in survival were achieved by optimising secondary prevention treatments compared with in-hospital reperfusion treatments (104 vs  $\leq$ 30 lives/10 000).<sup>98</sup> Recommended are aspirin,  $\beta$  blockers, statins, renin-angiotensin system blockers and thienopyridines—a study of 5353 patients showing that treatment with all five drugs reduced 1-year mortality by 74% compared with treatment with one or none of them, with consistent effects in STEMI and NSTEMI.<sup>99</sup> Evidence that statins and clopidogrel provide the greatest independent pharmacological benefit (ORs for death 0.85 (0.73 to 0.99) and 0.84 (0.72 to 0.99)) was provided by the GRACE investigators in a nested case-control study of 5148 patients with acute coronary syndromes,<sup>99</sup> and two separate studies have now reported the adverse consequences of failing to adhere to treatment with these drugs during the first year after discharge.<sup>100</sup> <sup>101</sup> The message is clear that prescribing secondary prevention treatment according to guideline recommendations and promoting adherence to treatment can together produce further mortality reductions in patients with myocardial infarction.

### Implantable cardioverter-defibrillators (ICDs)

Left ventricular ejection fraction (LVEF) after acute myocardial infarction remains predictive of sudden death in the primary PCI era<sup>102</sup> and is the key determinant of which patients should be offered an ICD for primary prevention.<sup>103</sup> However, LVEF in the acute phase is an unreliable guide to LVEF at 3 months when significant recovery of contractile function has often occurred.

But there is another reason for delaying decisions about ICDs beyond the guideline-recommended 40 days. Thus a recent randomised trial of ICD therapy in 898 patients with LVEF  $\leq$ 40%, recruited within 31 days of acute myocardial infarction, showed no overall mortality reduction for the patients who received an ICD because a high rate of non-sudden death negated protection against sudden arrhythmic death provided by the ICD.<sup>104</sup> A secondary analysis of DINAMIT has now confirmed a high risk of non-sudden death in patients who receive ICDs early after myocardial infarction, while the VALIANT investigators have reported that recurrent infarction or cardiac rupture are common causes of death during this period.<sup>105,106</sup> Taken together, these findings explain why ICDs fail to protect against death if implanted early after myocardial infarction. Decisions should, therefore, be deferred, and patients selected for ICD therapy according to measurement of LVEF at 40 days.

## Conclusion

The management of acute coronary syndromes continues to evolve and improve. The challenge for cardiovascular researchers is to maintain this momentum and to ensure that the improvements in outcome seen in the developed world have a global impact.

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