Acute coronary syndromes*

Charles Knight, Adam D. Timmis.

Barts and the London School of Medicine and Dentistry London Chest Hospital. London UK.

Received on September 8, 2011; accepted on September 15, 2011.
(As previously published in Heart)

Incidence and mode of presentation

Temporal trends for the global coronary epidemic vary by region but in most developed countries mortality is in decline. Life style 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. Smoking, a potent thrombogenic stimulus, is a major determinant of ST elevation myocardial infarction (STEMI) 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 non-ST elevation myocardial infarction (NSTEMI) increased by 30%. Overall, there was a 24% reduction in hospitalizations for acute coronary syndromes despite lowering of diagnostic thresholds by sensitive troponin biomarkers. 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 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.

Diagnosis

Diagnostic definitions of acute coronary syndromes are internationally agreed based on troponin release and symptomatic, electrocardiographic, or functional criteria. Troponins. Demonstration of a changing troponin concentration in the first 24 hours 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 has evaluated 4 high sensitivity assays in 718 patients with suspected ACS, 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. 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 ACS. Values below the previous limit of detection (0.20 ng/ml) -conventionally considered “normal”- showed graded association with death or nonfatal myocardial infarction, with rates of 7% and 39% for troponin concentrations of <0.05 ng/mL and 0.05 to 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 MI...
in patients with troponin concentrations 0.05 to 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 ACS and produce major improvements in their prognosis.

Other diagnostic biomarkers. Studies evaluating novel biomarkers for the early diagnosis of myocardial infarction have been the subject of recent systematic review. 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 for rule-out of myocardial infarction in the first 6 hours 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.

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 and myoglobin. RATPAC recruited 2243 patients with suspected myocardial infarction and randomized them to standard care or panel evaluation on admission to the emergency room and 90 minutes later. 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 sub study 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. 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. Only 3 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 myocardial 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. These data show that LBBB is of limited diagnostic utility in suspected myocardial infarction and provide a case for novel 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 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. 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 LV regional wall motion abnormality. A new diagnostic application for identifying those patients with NSTEMI who have complete coronary occlusions was recently described. In such patients circumferential strain measured within 1 hour of admission was independently diagnostic, values ≥10% showing 90% sensitivity and 88% sensitivity 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 as a means of guiding treatment and determining prognosis.

Clinical factors are used intuitively by clinicians. They recognize that risk increases with age and shows important gender differences, young women with STEMI, for example, having a 15% to 20% higher mortality risk than men. ECG criteria and routine biochemistry are also used for risk stratification, outcomes worsening with admission hyperglycaemia and also it seems with admission hypoglycaemia. 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.

Diagnostic biomarkers Increasing troponin release in NSTEMI is associated with a proportionate increase in risk of lethal arrhythmias, cardiogenic shock, new heart failure and death. CRP, the most widely studied prognostic biomarker, is also moderately predictive of adverse outcomes in acute coronary syndromes, a recent meta-analysis reporting a pooled relative risk of 2.18 (1.77 to 2.68) for the top (>10 mg/L) compared with the bottom (≤3 mg/L) category of values. 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 NT-proBNP, CRP, cardiac troponin I, and estimated glomerular filtration rate
(eGFR) provided incremental prognostic value to established risk indicators, except NT-proBNP for 6 week outcomes. Combining multiple biomarkers may improve predictive power for adverse outcomes but confirmation of incremental value over established risk scores is still awaited.

Risk scores. Validated risk scores based on a range of readily available factors currently 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 100686 cases of ACS its discriminative performance in predicting mortality compared favourably with a range of other risk models including PURSUIT, GUSTO-1, GRACE, SRI and EMMACE. The GRACE score appears to have lost none of its clinical value with the availability of high sensitivity cardiac troponin assays (hs-cTn). 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 inhospital and 1-year mortality, and addition of hs-cTn produced no improvement in the mortality prediction.

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. The drive towards primary PCI, based on evidence of a sustained mortality benefit compared with fibrinolysis, has been underpinned by the establishment of regional networks that have defined local standards of care and provided infrastructure for staffing heart attack centres.

Timely treatment is essential to maximize prognostic benefit, and important as it is to achieve door to balloon times within 90 minutes, other intrinsic delays within the healthcare process also need consideration. Thus, a Danish registry analysis of 6209 STEMI patients 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 a hazard ratio for mortality during the next 3.4 years of 1.22 (95% CI, 1.15-1.29; P < 0.001) per 1-hour increase in system delay. The findings emphasise the importance of minimizing transfer times from non-PCI hospitals and introducing policies of pre-hospital diagnosis to permit direct delivery of STEMI patients to interventional centers. 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.

Vascular access. Primary PCI by radial rather than femoral access is the preferred approach for an increasing number of operators. Its main advantage appears to be a lower rate of bleeding complications, the randomized RIVAL trial of radial versus femoral access in 7021 patients with ACS 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 hematomas and pseudoaneurysms. Findings were similar in a recent observational study of 1051 primary PCI cases with vascular complication rates of 0% and 1.9% for radial vs. femoral access. However, RIVAL found no outcome advantage for radial access and femoral access is still preferred by many operators because access is more predictable and procedure times may be shorter compared with the radial approach.

Stenting. Concerns about stent thrombosis led to recommendations for bare metal stents in primary PCI but randomized trials have now confirmed important advantages for drug eluting stents. The HORIZONS-AMI three year results showed lower rates of target lesion revascularisation for the 2257 patients randomized to paclitaxel eluting stents compared with the 749 patients randomized to bare metal stents (9.4% vs. 15.1%). 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 anti-platelet therapy 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 vs multivessel PCI. The main purpose of primary PCI is to achieve reperfusion of jeopardized myocardium by re-opening 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 randomized 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 compared with multivessel PCI whether performed during the primary PCI procedure or as better, as a staged procedure afterwards. This trial has now been included in a meta-analysis of 4 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. However, multivessel PCI during the primary procedure was associated with 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%). 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 pathologic 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. Magnetic resonance imaging has confirmed that thrombus aspiration reduces microvascular obstruction during primary PCI and limits infarct size at 3 months. A more recent analysis of pooled individual patient data from 3 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. 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. Consistent with this is a meta-analysis of thrombectomy trials showing that the mortality benefit for patients randomized to thrombus extraction is confined to patients treated with manual thrombectomy.

**Antiplatelet strategies** Current recommendations are for loading doses of aspirin and clopidogrel immediately prior to primary PCI followed by maintenance therapy. Adjunctive treatment with glycoprotein (GP) IIb/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 P2Y12 receptor more potently than clopidogrel are now available and have been evaluated in combination with aspirin in patients undergoing primary PCI. In the TRITON-TIMI 38 trial of dual antiplatelet therapy, prasugrel reduced the primary outcome of cardiovascular death, non-fatal MI 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.

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%). Strikingly, however, there appeared to be no cost in terms of 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 glycoprotein (GP) IIb/IIIa receptor blocker in STEMI patients undergoing primary PCI. Benefits appear to be inversely related to inflammatory burden and may be enhanced by intracoronary administration, a recent meta-analysis reporting improved clinical outcomes by this route. However, abciximab is expensive and there are now studies confirming non-inferiority of "small-molecule" GP IIb/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 (MI) during 1-year follow-up (15.0% vs. 15.7%). In a smaller study, 427 patients randomized either to eptifibatide or abciximab showed comparable rates of complete ST segment resolution 60 minutes after primary PCI (62.6% vs. 56.3%) with no significant differences between cardiovascular outcomes. In the On-Time2 trial, another small molecule compound, tirofiban, in combination with aspirin and clopidogrel provided more effective platelet inhibition compared with 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. 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 superior net clinical composite of death, MI, stroke, or major bleeding (10.8% vs. 9.4%; HR, 0.87; p = 0.008) in the subset of 19,085 patients treated invasively. A similar benefit was observed in patients treated conservatively. Fondaparinux is now widely used in preference to heparin in acute coronary syndromes.

**Bivalirudin** is a direct thrombin inhibitor that showed superiority to a combined regime of heparin plus a GP IIb/IIIa inhibitor in HORIZONS-AMI, due largely to a lower rate of major bleeding (4.9% vs. 8.3%). 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. 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 therapy**

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, yet a significant minority of patients in England and Wales continue to be treated with it. This may be justified if fibrinolysis can be delivered within 30 minutes after presentation when primary PCI is not immediately available, because treatment delays by either modality are associated with substantial increases in mortality. 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 re-infarction compared with in-hospital thrombolysis for patients with STEMI. The difference in re-infarction rates was only significant for tenecteplase (9.6% vs. 6.4%), not reteplase, and was particularly marked when transport times exceeded 30 minutes. It was attributed to differences in the use of adjunctive anti-thrombotic therapy in the two treatment
environments. Interestingly, bleeding complications were more frequent in the hospital-environment where adjunctive anti-thrombotic treatment was more aggressive, consistent with recent data from RIKS-HIL showing that major bleeding complications among patients receiving fibrinolytic therapy continued to increase from 2001-2006 as anti-thrombotic treatments became more effective.\textsuperscript{49} The current availability of potent ADP P2Y12 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.\textsuperscript{70,71}

The role of invasive treatment after fibrinolytic therapy 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.\textsuperscript{72,73} 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 elevation myocardial infarction (NSTEMI)**

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.\textsuperscript{4} There has been a perception that NSTEMI is relatively benign despite evidence that prognosis after 2 months becomes substantially worse than STEMI.\textsuperscript{21,74} This may explain the tendency of physicians to under-treat NSTEMI based on a mismatch between perceived and actual risk that distorts management decisions, perpetuating the “treatment-risk paradox”.\textsuperscript{25} Thus, despite a worse prognosis, patients with NSTEMI are less likely than patients with STEMI to receive optimal secondary prevention therapy.\textsuperscript{75} 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.\textsuperscript{76}

**Emergency management.** Dual antiplatelet therapy with aspirin and clopidogrel is central to the management of NSTEMI.\textsuperscript{77} The role of newer more potent ADP P2Y12 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.\textsuperscript{78} 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.\textsuperscript{79} 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 GP IIb/IIIa receptor blockers were co-prescribed\textsuperscript{80} and cost-effectiveness has now been confirmed.\textsuperscript{81} 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 GP IIb/IIIa receptor blocker or bivalirudin plus GP IIb/IIIa receptor blockers.\textsuperscript{82}

The majority of patients with NSTEMI benefit from interventional management,\textsuperscript{83} but recent data suggests this could be delayed at least 24 hours unless ongoing clinical instability unresponsive to GP IIb/IIIa receptor blockers calls for earlier action. Thus, in a randomized 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 (MI) or unplanned revascularisation, was significantly higher in the group receiving immediate PCI (60\% vs. 39\%).\textsuperscript{84} The difference persisted at 6 months’ follow-up. Delaying intervention beyond 96 hours is unlikely to be helpful, yet registry data show that this is common, particularly in high risk patients who have most to gain from revascularization.\textsuperscript{85} The evidence for timely revascularisation is largely based on PCI data but a small proportion of patients require CABG. An analysis of US registry data showed that the timing of CABG had 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 was done within 48 hours of admission or later.\textsuperscript{86} In general, therefore, early surgery is recommended to limit hospital stay and reduce resource utilization.

**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.\textsuperscript{87} 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\% to 85\%.\textsuperscript{88} Reasons for the poor uptake are complex but include the fact that many patients do not want to participate in centre-based group programs. A systematic review has now reported that home-based programs are equally effective in improving clinical and health related quality of life outcomes and are more acceptable to many patients.\textsuperscript{89} Healthcare costs are similar supporting the further provision of home based cardiac rehabilitation such as that described by investigators in Birmingham.\textsuperscript{90} 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.\textsuperscript{91}

**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 showing that the adjusted hazard ratio for all-cause mortality was lower by 43\% in lifelong nonsmokers and by 43\% in patients who quit after myocardial infarction.\textsuperscript{92} A novel finding was that among
persistent smokers each reduction of 5 cigarettes smoked per day reduced the risk of death by 18%, providing some comfort for those patients in 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.\textsuperscript{93} The message is clear that protection against recurrent events in survivors of myocardial infarction requires smoking cessation not only by the patient but also by those with whom the patient makes contact, particularly family members.

When smoking cessation, and advice about exercise and diet are delivered in formal programs it can have a salutary effect on modifiable risk profiles, including serum cholesterol, blood pressure and body mass index.\textsuperscript{94} Dietary recommendations usually include omega-3 fatty acid supplements\textsuperscript{95} but this has now been questioned by the findings of 2 studies. In the first, 4837 patients with previous myocardial infarction were randomized to margarines containing marine n–3 fatty acids and plant-derived alpha-linolenic acid (ALA) in a 2 x 2 factorial design.\textsuperscript{96} 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.\textsuperscript{97} 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.

\textit{Pharmacotherapy} The importance of optimal secondary prevention after myocardial infarction was emphasized in a modeling study in which greater absolute gains in survival were achieved by optimizing secondary prevention treatments compared with in-hospital reperfusion treatments (104 vs. ≤30 lives/10,000).\textsuperscript{98} Recommended are aspirin, beta-blockers, statins, renin angiotensin system (RAS) blockers and thienopyridines, a study of 3535 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.\textsuperscript{99} Evidence that statins and clopidogrel provide the greatest independent pharmacologic benefit (odds ratios 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 ACS patients,\textsuperscript{100} 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.\textsuperscript{101,102} 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.

\textit{Implantable cardioverter defibrillators (ICDs).} Left ventricular ejection fraction (LVEF) after acute myocardial infarction remains predictive of sudden death in the primary PCI era\textsuperscript{103} and is the key determinant of which patients should be offered an ICD for primary prevention.\textsuperscript{104} 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 ≤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.\textsuperscript{105} 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.\textsuperscript{106,107} 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.

\section*{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 develop a global impact.

\section*{References}


43. Patterson T, Foale RA. If the radial artery is the new standard of care in primary percutaneous coronary intervention, why is most intervention done by the femoral approach? Heart 2011;97:521-552.


47. Politli L, Sgura F, Rossi R, et al. A randomised trial of target-ve-


55. Haeck JD, Kuitj WJ, Koch KT, et al. Infarct size and left ventricu-


62. Akerblom A, James SK, Koutouzis M, et al. Epitfbatide is no-

63. Zeymer U, Margenet A, Haude M, et al. Randomized comparison of epitfbatide versus abciximab in primary percutaneous coronary inter-


65. Mehta SR, Boden WE, Elkeiboom JW, et al. OASIS 5 and 6 inves-


70. Steg PG, James S, Harrington RA, et al. PLATO Study Group. Ticagrelo versus clopidogrel in patients with STElevation acu-

71. Wijeyesundera HC, You JJ, Nallamothu BK, et al. An early inva-


74. Bramlage P, Messer C, Bitterlich N, et al. The effect of optimal medical therapy on 1-year mortality after acute myocardial in-

75. Knight Ch et al
87. Hammill BG, Curtis LH, Schulman KA, et al. relationship bet-
trial comparing home-based with centre-based cardiac rehabili-
91. Lee BC, Hsu HC, Tseng WY, et al. Effect of cardiac rehabilita-
107. Pouleur AC, Barkoudah E, Uno H, Skali H, et al. VALIANT Investi-