Cardiology series — 3

# Contemporary themes in acute coronary syndrome management: from acute illness to secondary prevention

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## Summary

- Acute coronary syndrome (ACS; myocardial infarction and unstable angina) is the leading cause of mortality in Australia, and those who survive one ACS event are at significant risk of experiencing another.
- Access to evidence-based and optimal ACS management in both the acute and long-term periods is of great importance. Management of ACS should include appropriate timely revascularisation, medical therapy and ongoing secondary prevention.
- A key consideration in selecting acute antithrombotic therapies is a careful determination of the risk of bleeding versus risk of recurrent ischaemia.
- Although there is a strong evidence base for the urgency of delivery and the quality of acute care, knowledge translation is suboptimal. There remains a need for ongoing research and policy development aimed at improving ease and equity of access to evidence-based care.
- Despite universal guideline recommendations for ongoing secondary prevention strategies, research indicates suboptimal use of evidence-based medications, poor adherence to lifestyle recommendations, and low levels of participation in traditional cardiac rehabilitation.
- Contemporary secondary prevention programs are evolving into flexible, multifaceted interventions to provide maximal clinical benefits to a majority of patients.

Acute coronary syndrome (ACS; myocardial infarction and unstable angina) is the leading cause of mortality in Australia and accounts for more than 300 000 years of life lost due to premature death (aged < 65 years) annually. The cost of repeat ACS events in 2010 exceeded $8 billion.[1] About half of the cardiovascular events in Australia occur in people who have had a prior hospital episode for coronary heart disease (CHD).[2] Therefore, access to evidence-based and optimal ACS management in both the acute and long-term periods is of great importance.

In recent years, advances in monitoring, revascularisation and pharmacotherapy for acute illness have contributed to a reduction in mortality. However, a quarter of these survivors will be readmitted to hospital within a year of the index event, and a significant number of readmissions will result in death.[3,4] Consequently, the demand for effective secondary prevention is intensifying, and ensuring access to structured management strategies that complement standard medical care is now a priority.

The burden of CHD is disproportionately greater for certain patient groups. People living in outer regional and remote areas experience disease rates 20% higher than do those living in major cities, with higher mortality proportionate to increasing distance from major centres.[5] Cardiovascular disease is also the largest contributor to the 17-year gap in life expectancy between Indigenous and non-Indigenous Australians.

Here, we provide an overview of key contemporary issues in the provision of ACS care, including the importance of early diagnosis of ischaemia; risk stratification; provision of timely, appropriate and evidence-based management; and prevention of recurrent events. We describe barriers to the equitable provision of immediate and long-term optimal care and suggested strategies to overcome them. These strategies focus on the practice and policy changes needed to implement networked systematic care across all geographical and economic strata serviced by our health care system.

## Contemporary considerations for ACS management

Contemporary management of ACS should be rapid and should include reperfusion, medical therapy and ongoing secondary prevention. Management should be comprehensive, coordinated and ongoing. Ideally, patients should seek medical care as early as possible after the onset of symptoms and should be provided with: rapid access to a hospital or a defibrillator; early reperfusion therapy for ST-segment-elevation myocardial infarction (STEMI); early angiography and revascularisation where indicated; appropriate medical therapy; and ongoing secondary prevention that encompasses medication adherence and lifestyle change.[6]

### Rapid reperfusion for STEMI

STEMI accounts for about 25% of ACS presentations and remains a cardiac emergency. As rapid restoration of epicardial blood flow is of initial importance,[6] the first goal of therapy is immediate reperfusion, which is best achieved by primary percutaneous coronary intervention (PCI) when appropriately staffed facilities are available.[7] If delays are likely because of the need to transfer patients long

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**1 Indications and precautions for the newer orally active ADP receptor antagonist antiplatelet agents***

| Agent | Indications | Precautions |
|---|---|---|
| Prasugrel | ST-segment-elevation myocardial infarction with planned percutaneous coronary intervention (PCI)<br>Non-ST-segment-elevation acute coronary syndrome undergoing PCI | Contraindicated in patients with previous stroke or transient ischaemic attack<br>Caution in patients aged over 75 years or weighing under 60 kg (increased bleeding; consider reduced maintenance dose) |
| Ticagrelor | All acute coronary syndromes | Caution in patients with second- or third-degree heart block<br>Caution in patients at increased risk of bleeding (although these patients are often also at high risk of recurrent ischaemic events) |

* This list of precautions is not exhaustive; consult a full list before prescribing. ◆

distances for primary PCI, fibrinolysis is a superior option, particularly for patients receiving medical attention early after the onset of symptoms.[6,7] Fibrinolysis can be of substantial value in the rural prehospital setting, where delays to PCI are unavoidable. For patients with large infarcts receiving fibrinolysis in non-PCI-capable centres, early transfer (ideally within 24 hours) to a PCI-capable centre for coronary angiography is now recommended.[8] This enables emergency treatment (rescue PCI) for patients who have not reperfused after fibrinolysis. For those who have reperfused, emergency PCI is best performed from 3 to 24 hours after lysis; this minimises both the access-site bleeding consequences of the lytic therapy and the likelihood of culprit vessel reocclusion.

### An invasive management strategy for non-ST-segment-elevation ACS

Patients with a non-ST-segment-elevation ACS and who are at high risk of inhospital and late death or myocardial infarction benefit from coronary angiography, which guides an appropriate revascularisation strategy during their hospital stay.[9] The earlier this procedure is performed, the greater the benefit.[10] Lower-risk patients may be risk stratified through either angiography or non-invasive testing. Intervention-related bleeding can be reduced by adopting a radial rather than femoral approach to coronary angiography. The radial approach may also be associated with reduced mortality in the STEMI population,[11] and this strategy is gaining in popularity.

### Medical therapy

Antithrombotic strategies using heparin or low-molecular-weight heparin remain a cornerstone of therapy to prevent propagation or embolisation of the thrombus responsible for the coronary instability. However, iatrogenic bleeding events, traditionally regarded as a tolerable complication of anti-ischaemic therapy, are themselves associated with increased mortality.[12] Newer anticoagulant agents, such as fondaparinux and bivalirudin, can reduce recurrent ischaemic events with comparable efficacy and less bleeding than traditional heparins among medically managed and PCI-managed ACS patients, respectively.[13,14] Where increased bleeding risk is anticipated, these newer therapies are recommended.[8]

In addition to anticoagulants, dual antiplatelet therapy with low-dose aspirin and the ADP receptor antagonist clopidogrel is associated with reduced ischaemia in patients after an ACS when compared with aspirin alone.[15] More potent ADP receptor antagonists, such as prasugrel and ticagrelor (Box 1), prescribed as substitutes for clopidogrel, extend this benefit further, but do so at the cost of increased bleeding.[16,17] Here, the risk–benefit equation is more complex because these newer agents have improved efficacy with a possible reduction in mortality,[17] underscoring the need for a better understanding of the prognostic impact of different types of bleeding (eg, access-related versus gastrointestinal), together with more sophisticated tools to predict bleeding.

### Emerging acute treatments

Reperfusion after coronary occlusion is associated with the release of products that are toxic to injured but perfused myocardial cells. Over the past 40 years, many therapeutic strategies have been trialled, unsuccessfully, to prevent reperfusion injury. Strategies for which there is cautious optimism include intracoronary adenosine, hypothermia, and "conditioning" the myocardium by alternating periods of brief ischaemia and reperfusion.[18,19] Early studies indicate that infusing a patient's own stem or progenitor cells in the infarct setting may promote restoration of myocardial function.[20,21] Larger trials with standardised methodology are required to establish the role of this therapy.

### Secondary prevention

In the transition to primary care after hospital discharge, ongoing participation in a secondary prevention program is recommended for all ACS survivors.[22] Attending secondary prevention programs, adhering to risk factor modification and complying with drug regimens may reduce hospital readmissions within 1 year by 45% and increase survival.[23] Advances in secondary prevention approaches include clinic-based coordinated care, individualised case management and coaching with regular monitoring and, more recently, e-health strategies that provide flexible ongoing care.[4]

Secondary prevention ideally requires a lifelong commitment to ongoing behaviour change. The original model for delivery of "cardiac rehabilitation" to patients with CHD focused on supervised exercise to counter deconditioning after bypass graft surgery and to improve exercise capacity after myocardial infarction. However, patients are no longer confined to long periods of bed rest after an ACS event, and their needs are different than when traditional programs were developed. Around 70% of secondary prevention programs offered in Australia continue to follow the traditional cardiac rehabilitation model of structured, group-based exercise and education delivered in a hospital setting.[24] However, traditional facility-based cardiac rehabilitation is currently facing substantial challenges in terms of access, appeal and cost. Non-attendees are returning to work commitments early and are less likely to believe that rehabilitation is necessary, despite having higher baseline risk and poorer risk factor knowledge than those who do attend.[25] Evidence that hospital-based secondary prevention interventions are effective[26] is now supplemented by evidence that programs can be provided in various settings, by different health professionals, and in various ways.[4] The development of contemporary flexible models

**2 Australian case studies of acute coronary syndrome (ACS) management**

**Case study 1: ST-segment-elevation myocardial infarction**

A 64-year-old man (Mr T) was driven by his wife to the emergency department (ED) of a rural hospital 2 hours after onset of retrosternal chest discomfort. He had a 12-month history of exertional angina, was a retired office worker and did not participate in regular exercise. His local general practitioner, whom he generally saw "as little as possible", had recommended smoking cessation and medical treatment with aspirin, a statin and long-acting nitrates. Mr T had managed to reduce his smoking to five cigarettes/day, had not liked the statin (it gave him muscle pain), took aspirin intermittently and had stopped taking the nitrates (they gave him a headache).

Within 20 minutes of arrival at the ED, an electrocardiogram (ECG) showed ST-segment elevation in the anterior leads. The resident faxed the ECG to the coronary care unit at the nearest base hospital, where it was reviewed by a medical registrar, who discussed it with the on-call physician. The resident was instructed to administer thrombolysis with tenecteplase (TNK), which was delivered 90 minutes after Mr T's presentation to the hospital. Within 30 minutes, his chest pain settled, and the ECG results improved. Staff at the rural hospital phoned the nearest tertiary hospital (with cardiac catheterisation facilities) to arrange a transfer. This hospital was a 4-hour drive away and had no available coronary care beds.

Forty-eight hours after initial presentation, Mr T experienced recurrent pain accompanied by further ST-segment elevation. A second dose of TNK was given, and he was transferred to the tertiary hospital. Coronary angiography showed a 90% lesion with reduced flow in the proximal left anterior descending coronary artery, a 70% lesion in the left circumflex artery and a 60% lesion in the right coronary artery. Mr T was referred for coronary artery bypass grafting, which was performed during the same admission. He was discharged 5 days later with a medication regimen of aspirin, frusemide and an angiotensin-converting enzyme (ACE) inhibitor. While in hospital, he was seen by a cardiac rehabilitation nurse, who provided some written information about heart disease and a letter for his GP. The hospital did not arrange an appointment with the GP.

**Case study 2: Non-ST-segment-elevation ACS**

A 75-year-old woman of Italian origin (Mrs D), who had been in Australia for 15 years but had poor command of English, called an ambulance 3 hours after developing intermittent nausea and diaphoresis. She had experienced similar symptoms before undergoing a coronary artery bypass graft 10 years earlier and had noticed recurrence of these symptoms on exertion for the past 2 weeks. Mrs D had been diagnosed with atrial fibrillation 5 years earlier when she presented with heart failure. She had been taking warfarin since then, and was also taking frusemide and an ACE inhibitor, but no statin.

The ambulance took Mrs D to the nearest hospital, which did not have percutaneous coronary intervention (PCI) facilities. Her symptoms had settled by the time of arrival. Examination showed mild left ventricular failure (crepitations in the lower third of the lung fields), an ECG showed a non-specific intraventricular conduction delay, and her troponin level was normal. Measurement of the troponin level was not repeated. Her creatinine level was elevated (165 μmol/L [reference interval, 60–115 μmol/L]). She was diagnosed with possible unstable angina and commenced taking aspirin and a nitrate, with a plan for 48 hours of observation followed by discharge for outpatient functional study. On her second day in hospital, Mrs D developed recurrent symptoms with pulmonary oedema, which responded to continuous positive airways pressure and diuretic therapy. Arrangements were made for coronary angiography at the nearest PCI-capable hospital. She was transferred 4 days later (once her international normalised ratio [INR] had fallen to < 1.5). Coronary angiography showed a stenosed vein graft to a circumflex vessel, which was treated with a 3.5 mm drug-eluting stent.

Mrs D was discharged 5 days later (once her INR had reached 2) with a medication regimen of aspirin, clopidogrel, warfarin, frusemide, an ACE inhibitor and a statin. The hospital arranged an appointment with her GP. Eighteen months later, she re-presented to the hospital with a massive gastrointestinal bleed. At this time, she was still taking aspirin, clopidogrel and warfarin. ◆

that use existing community services (eg, government "quit smoking" programs, the Enhanced Primary Care Program, National Heart Foundation of Australia physical activity initiatives, and private health insurer programs) are examples of this.

## Evidence–practice gaps in Australian ACS management

Deficits in the application of optimal ACS care occur in the prehospital, inhospital and postdischarge periods. The case studies outlined in Box 2 highlight some of these contemporary issues.

### Delays in reperfusion for STEMI

In the first case study, Mr T experienced delays in presentation to hospital and in the performance and interpretation of the electrocardiogram (ECG), which significantly delayed time to reperfusion. Australian evidence suggests that patients with STEMI wait a median time of 100 minutes before seeking medical attention, and this delay has not changed since it was first described in the early 1990s. A significant proportion of patients with STEMI do not receive timely reperfusion after presentation to hospital (within 90 minutes of presentation for PCI, and 30 minutes for fibrinolysis).[27] Overcrowding of emergency departments and access block can contribute to this delay.[28] This means there is a median delay from symptom onset to reperfusion exceeding 190 minutes for patients receiving PCI and 130 minutes for those receiving fibrinolysis — times well beyond the threshold for the development of significant irreversible myocardial necrosis.

Of equal concern is that about 30%–40% of all patients with STEMI receive no reperfusion therapy.[3] It has been estimated that increasing the numbers of patients treated with reperfusion therapy would save 270 lives per 10 000 patients with STEMI.[6]

### Access to and appropriate application of invasive management

If Mr T had been transferred to a PCI-capable centre within 24 hours after receipt of fibrinolytic therapy, he could have had early angiography, which would likely have prevented his recurrent myocardial infarction. Similarly, had Mrs D been recognised as being at high risk of a recurrent event, she could have received earlier coronary angiography. There are well validated bedside tools[29] that predict the likelihood of inhospital events and guide the application of appropriate management. However, these tools are rarely applied in Australian hospitals. There is also geographical heterogeneity in the provision of coronary angiography for ACS patients in Australia.[30] Where access to coronary angiography is available, risk-averse physician behaviour is observed, whereby the highest-risk patients with the most to gain from invasive management are the least likely to receive it.[31] Clinicians select therapy on the basis of acute risk factors (ECG changes and troponin level elevation), while patients accumulating chronic risk factors are less likely to receive evidence-based therapies.[32]

### Poor access to and uptake of secondary prevention

Mr T was discharged with suboptimal secondary prevention therapies, some written information and a letter for his general practitioner. At the time of discharge, there was no strategy for ensuring he complied with these instructions.

A 2005–2007 Australian audit showed that only a minority of patients with ACS received all five guideline-recommended secondary prevention treatments at hospital discharge.[33] Although there have been some improvements, gaps remain[3] and there is a lack of recognition of this problem by clinicians. Australian general practice surveys show that only half of patients with established CHD take recommended treatments.[34] Only about a third of patients adhere to recommendations on diet, exercise and smoking, and participation rates in cardiac rehabilitation programs are as low as 10%–30%.[35]

Failure to follow guidelines can result in errors of commission, as well as errors of omission. Mrs D continued taking "triple therapy" (warfarin and two antiplatelet agents) for 18 months after coronary stenting. Current recommendations minimise the duration of this

**3 Strategies aimed at increasing access to secondary prevention**

- Automatic referral of all eligible patients
- Availability of different program types, including home, primary care, hospital and community-based strategies
- Use of e-health, including communication by telephone, email, the internet or videoconferencing
- Provision of programs that involve family-based strategies
- Coordinated care comprising medical visits with general practitioners and specialists in combination with participation in a structured secondary prevention program ◆

combination therapy to reduce the risk of bleeding.[36] The fact that this did not occur further illustrates the lack of fluidity between tertiary and primary care.

## Overcoming the deficits

An integrated and multifaceted strategy that targets both the public and our systems of health care delivery is needed. Some strategies implemented in the Australian context have been shown to be effective. For example, educating the public to recognise symptoms of a heart attack has been a major focus of the National Heart Foundation of Australia's "warning signs" campaign, which has run since 2008.[37] Empowering ambulance service personnel to perform and interpret 12-lead ECGs at first patient contact allows for the immediate identification of STEMI. Reports from clinical cardiac networks in both New South Wales and Victoria have shown the benefit of prehospital diagnosis and triage.[38,39] The introduction of the National Emergency Access Target to overcome issues of access block and emergency department overcrowding is an important organisational strategy that facilitates timely ACS management in busier centres. Furthermore, the creation of local hospital networks has provided a substrate for optimising interhospital transfers. If STEMI is identified in a patient self-presenting to a non-PCI-capable centre, it is possible to facilitate near-immediate transfer to a notified nearby PCI-capable hospital. Strategies to minimise transfer (door-in–door-out) time include ambulance prioritisation of these patients, and standardised protocols for STEMI reperfusion at both referring and receiving hospitals.[40] Using combined geographical, road transport time and census data, researchers have estimated that implementing improved efficiencies, such as prehospital ECG diagnosis and triage and facilitated interhospital transfers, can improve access to timely reperfusion for more than five million Australians.[41]

One of the greatest challenges facing hospital clinicians is identifying high-risk patients and stratifying treatment accordingly. Several clinical networks are now providing systematic rural ECG reading services, with the provision of clinical advice to support rural clinicians. Additional strategies include using telemedicine to empower rural GPs to read ECGs. Beyond this, studies investigating the prognostic benefit of routine application of risk stratification tools are planned locally. Interhospital transfer for identified high-risk patients can be facilitated by real-time, web-based interhospital catheter laboratory triage systems. In Queensland, this has been associated with a dramatic improvement in timely appropriate transfer of patients from non-PCI-capable to PCI-capable hospitals.

Universal prescription of evidence-based secondary prevention therapies remains challenging and can only partly be addressed by medication reconciliation at discharge. In one Australia-wide study, the introduction of clinical tools, together with academic detailing of selected clinical staff, had a modest effect on the prescription of evidence-based therapies.[42] It appears that hospital culture is the most important determinant of whether improvements in care processes are successful. An effective culture is one that values quality improvement and has clinical leadership, senior management involvement, and good communication between the various clinical groups responsible for providing care.[43]

Transitioning from the acute to the postdischarge phase can be facilitated by automatic referrals and availability of a range of innovative secondary prevention programs (Box 3).[26] These programs frequently involve (in isolation or combination) in-person visitations, community services, and home manuals with telephone or electronic support for flexible and individualised management of CHD. They include clinic nurse-coordinated care,[44] individualised case management and monitoring with periodic follow-up,[45,46] and community-based groups with ongoing health practitioner support provided across a range of settings.

To achieve optimal and sustainable benefits for the majority of patients, secondary prevention strategies must be flexible; tailored to the individual's preferences, needs and values; lifelong; and integrated with primary care.[6,47] All contemporary secondary prevention programs should include individual patient assessments and structured follow-up, as well as ongoing support and monitoring. Programs should target medication adherence, coupled with biomedical and lifestyle risk factors, while also attending to psychosocial wellbeing. Further, they should recognise the role of patients in self-management and the importance of family and caregiver engagement and support.[4]

## Future innovations

While the dominant pharmaceutical-derived research funding streams will continue to be directed towards newer therapies, the real impact of these is becoming limited as absolute event rates fall. Greater practical gains will be achieved through more widespread application of existing therapies. Improving information technology infrastructure has the potential for great impact on geographical inequities through the availability of clinical support systems (remote ECG interpretation and efficient web-based triage for interhospital transfer).

Many of the available data regarding the quality of patient care have been derived from clinician-driven clinical registries that are restricted by small patient numbers and hospital selection biases.[3,30,33] Only through a national ACS registry will we be able to truly understand the patterns and gaps in treatment around the country. In the short term, these data can be acquired through manual data extraction performed at a "snapshot" in time. However, this is resource- and labour-intensive, and as the electronic medical record environment matures, there will be opportunities to collect and audit performance measures and outcomes using clinically collected data. There are ethical, governance and data quality issues that require

careful attention; however, principles for the conduct of these registries have been established.[48] More mature electronic medical record technology will also help bridge the divide between hospitals and primary care.

Resources need to be allocated to permit the application of a national approach to secondary prevention, encompassing the variety of services outlined here, but unified by a patient-centred focus. Ultimately, a cohesive approach that is accessible, standardised and evidence-based is needed to improve widespread effectiveness.

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