Management of acute coronary syndrome in special subgroups: female, older, diabetic and Indigenous patients

Brendan M McQuillan
MB BS, PhD, FRACP
Associate Professor,[1] and Cardiologist[2]

Peter L Thompson
MD, FRACP, FACC
Clinical Professor,[1] and Cardiologist and Head, Heart Research Institute[2]

1 School of Medicine and Pharmacology, University of Western Australia, Perth, WA.
2 Sir Charles Gairdner Hospital, Perth, WA.

peterlthompson@health.wa.gov.au

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While guidelines for the management of acute coronary syndrome (ACS) for the average patient are well defined, their application to special groups is less clear. Some groups have been underrepresented or formally excluded from the clinical trials that constitute the evidence base that guides therapy, and some have special needs that have not been studied in clinical trials. As a result, these subgroups present clinical challenges for which there is weaker evidence to define appropriate management.

This article will assess the special needs of women, older people, patients with diabetes, and Aboriginal and Torres Strait Islander Australians.

Summary

- While the evidence base for management of acute coronary syndrome (ACS) is extensive, some subgroups have been underrepresented or excluded from relevant clinical trials.
- These subgroups — such as women, older people, diabetic patients and Indigenous Australians — present clinical challenges for which there is limited evidence to guide optimal therapy.
- Women may have a different pattern of presentation, with potential for delays in diagnosis and worse outcomes in ST-elevation myocardial infarction, but there is no evidence that treatments affect them differently from men.
- Older people suffer from a high-risk, low-treatment paradox. This may be due to under-appreciation of the benefits of treatments for older people, or to good clinical judgement in avoiding harm from worsening age-related comorbidities.
- Patients with diabetes have a high risk of ACS and suffer worse outcomes. Moderate glycaemic control with close monitoring and avoidance of hypoglycaemia are recommended. Coronary artery bypass grafting is preferred to percutaneous coronary intervention for patients with diabetes and multivessel disease, although the latter is reasonable in single-vessel disease.
- Indigenous patients have a high prevalence of coronary disease, with more frequent coronary events at a young age, a heavy load of risk factors and poor outcomes after ACS. The complex sociocultural barriers to treatment are yet to be addressed adequately.

Women

Cardiovascular disease remains the leading cause of death in women, and far exceeds deaths from cancer at all ages. Despite the popular perception that heart attack is far more common in men than women, this is true only in younger age groups. Across the full spectrum of age, women account for a large proportion of patients with ACS, comprising up to 45% of patients in some series[1] and 40% in a comprehensive snapshot of admissions to coronary care units in Australia and New Zealand in 2012.[2]

There is considerable evidence that the pattern of coronary disease and ACS is different in men and women.[3,4] Women tend to have less obstructive coronary artery disease and a higher prevalence of microvascular coronary dysfunction,[5] leading to the suggestion that the term *ischaemic heart disease* may be more appropriate for women than *coronary artery disease*.[6]

While most women presenting with an ACS will experience typical anginal symptoms, women are less likely to report chest pain or discomfort compared with men. They are more likely to report associated symptoms including dyspnoea, nausea and fatigue.[7] These differences may be partly explained by the higher average age at ACS presentation among women, with older patients of both sexes less likely to report chest pain.[7] There is a higher prevalence of stress or takotsubo cardiomyopathy among women, usually in the absence of obstructive coronary disease.[8] There are also some differences in the reference range and pattern of troponin elevation between the sexes.[9] Overall, however, the diagnostic and prognostic performance of troponins is similar in men and women.[10] These differences complicate the diagnosis of ACS in women, and may contribute to delays or deficiency in the delivery of guideline-indicated therapies.

The outcomes after an ACS are worse for women than men.[11] The most likely explanation is that women have their heart attacks about a decade later in age than men. After detailed multivariate analysis of age and other prognostic factors, being female is not an independent risk factor for non-ST-elevation ACS (NSTEACS), but it is for ST-elevation myocardial infarction (STEMI).[12] This disparity in STEMI is particularly evident in younger women (<55 years old), who have a higher risk of death and recurrent events compared with similarly aged men.[13,14]

Concerns have been expressed that women may not receive the same benefit from invasive management as men experiencing an NSTEACS. Individually, the trials comparing conservative with invasive management were each underpowered to demonstrate a benefit in women. Reports from meta-analyses of the trials give conflicting results. Trials to 2008 showed a clear benefit in women at higher risk,[15] but a more recent meta-analysis including the data from the OASIS 5 trial failed to demonstrate any benefit for women from an early invasive approach.[16] It is clear that women receive invasive management less frequently than men, probably because of higher rates of comorbidity rather than a treatment bias,[17] but do not fare any worse solely because of a lower rate of intervention.[18]

Women are less likely to receive guideline-indicated pharmacotherapies after ACS. The clinical trials for guiding pharmacotherapy after an ACS episode have tended to include far fewer women than men. As a result, the

evidence base to guide therapy in women is less robust than for men.[19] Despite this, there is no clear evidence that the usual post-ACS medications are less efficacious in women than in men. The available evidence shows equivalent efficacy for the post-ACS use of aspirin,[20] clopidogrel[21] and ticagrelor,[22] as well as the short- and long-term use of β-blockers,[23] statin therapy[24] and angiotensin-converting enzyme inhibitors[25] after myocardial infarction. Due to generally lower body weight and estimated glomerular filtration rates, especially among older women, caution is required to avoid excess dosing of antithrombotic therapy. Meta-analysis of the available clinical trials of hormone replacement therapy has shown no benefit, but no adverse effect of hormone replacement therapy after ACS.[26]

Older people

Older people comprise a large proportion of patients with ACS. In the United States-wide CRUSADE study, patients aged 75 years and older comprised 35% of all ACS patients.[27] The risk of a poor outcome after ACS rises with age, and each of the widely used scoring systems shows a major influence of age. In the Thrombolysis in Myocardial Infarction (TIMI) score for STEMI patients, an age of 75 years or older had an adjusted odds ratio of 2.7 for predicting 30-day mortality.[28] In the Global Registry of Acute Coronary Events (GRACE) score for patients with NSTEACS, each decade of increasing age was associated with an adjusted odds ratio of 1.7 for predicting 30-day mortality, with those aged 75 years having an eightfold higher risk of death at 30 days compared with a 40-year-old.[29,30] In 8557 patients from Australia and New Zealand enrolled in the LIPID Study, the rate of death or myocardial infarction over a mean of 6 years was 19.6% in patients aged 70 years and older compared with 11.2% in patients younger than 60 years, with a hazard ratio of 1.89 (95% CI, 1.60–2.23).[31]

Because of their higher absolute risk of adverse cardiovascular events after ACS, patients aged 75 years and older have potentially more to gain from appropriate therapies if they offer similar risk reduction across all ages. Despite this, there is a well recognised paradox that older patients who are at highest risk often receive less active treatment. The tolerability, safety and adverse event profile of these therapies must also be carefully considered for older patients. Clinical trials have enrolled lower proportions of older patients, with lower rates of comorbidities especially renal impairment, stroke and congestive heart failure, than are present in community series.[27] The proportion of patients presenting with atypical symptoms or non-diagnostic electrocardiogram changes increases with age, which may result in delays in the diagnosis of ACS and institution of appropriate therapies.[32] Patients' preferences and their perception of risks associated with invasive management must also be taken into account.

Although concerns regarding bleeding risks and vascular complications including stroke may explain lower rates of invasive strategies among older patients with ACS, similar patterns are observed for pharmacotherapy. Although each of the evidence-based post-ACS treatments has been shown to be effective for older patients,[33] there may be a reluctance to treat this group. Some of the reluctance for intervention and pharmacotherapy in older patients no doubt reflects sensible clinical judgement, as there may be increased risks with some medications with age.

The relative benefit of aspirin does not appear to be affected by age. Compared with younger patients, people aged 65 years and older had a greater absolute reduction in vascular end points and lower death rate with aspirin use after ACS.[34] For inhibitors of adenosine diphosphate-dependent platelet aggregation, when added to aspirin in the management of ACS, there is divergence in the risk–benefit profile for older patients. Clopidogrel offers similar absolute risk but lower relative risk reduction when given to patients older than 65 years compared with younger patients, although in both groups clopidogrel is more effective than placebo.[35-37] Patients aged 75 years and older and those with a body weight below 60 kg demonstrated no net clinical benefit from prasugrel in the TRITON–TIMI 38 study of ACS patients with scheduled percutaneous coronary intervention (PCI).[38] Those with prior stroke or transient ischaemic attack, which are more prevalent among older patients, had net harm with prasugrel. Ticagrelor was superior to clopidogrel in the overall PLATO trial, and has been shown to be of similar efficacy in reducing subsequent cardiovascular events among patients aged 75 years and older compared with younger patients.[39] Bleeding rates were similar to those with clopidogrel in patients 75 years and older and not significantly different to rates in those younger than 75 years included in PLATO. Dyspnoea and ventricular pauses were more common with ticagrelor, but at similar rates regardless of age.

Statins for secondary prevention of cardiovascular events have consistently demonstrated benefit compared with placebo, with most trials finding greater absolute risk reduction among patients aged 65 years and older compared with those younger than 65 years.[40] These findings have been extended in the PROSPER[41] and Heart Protection[42] studies, which included larger numbers of patients aged 75–80 years, with similar event reduction in each of the age groups. Meta-analysis of statin trials examining the benefit of more versus less aggressive lowering of low-density lipoprotein cholesterol levels for secondary prevention of cardiovascular events has shown similar efficacy in those aged older than 65 years compared with patients aged 65 years and under.[43] For ACS trials, efficacy has been shown with high-dose atorvastatin compared with lower-dose atorvastatin[44] or pravastatin,[45] without evidence of differential treatment benefits due to age. Statin therapy may have more side effects in older patients, particularly in higher doses, and closer surveillance is warranted.[46]

Older patients also have a higher likelihood of renal dysfunction that is not necessarily identified from serum creatinine levels,[47] and some studies estimate that significant renal dysfunction is present in up to 35% of people over the age of 70 years.[48] The likelihood of worsening renal dysfunction from use of contrast medium can be a factor in decision making for older patients who are being considered for invasive therapy.[49] Many cardiovascular

drugs are cleared by renal mechanisms, and dosing considerations should be observed.[50] Renal dysfunction can also be a significant factor in increasing the risk of bleeding with anticoagulants, particularly with low-molecular-weight heparins, which are cleared via the renal route.[51,52] Registry data show that excessive doses of antithrombotic agents are frequently given to older patients.[50]

Routine invasive therapy, which has a well recognised benefit in reducing myocardial infarction and recurrent angina compared with a selective invasive strategy,[53] can have an even greater benefit in older patients at high risk. The TACTICS-TIMI 18 trial compared the impact of invasive and conservative strategies in younger (aged 65–75 years) and older (aged over 75 years) patients. The early invasive strategy conferred an absolute reduction in end points of 10.8% in younger patients, and 21.6% in older patients ($P = 0.016$).[54] Despite this evidence of greater benefit, international[55] and Australian[56,57] studies have shown that older patients at higher risk routinely receive less invasive management than younger patients.

Explanations for this paradox in the delivery of invasive therapy vary, but there are valid clinician concerns about comorbidities, interaction with concomitant medications and increased fragility, which are more likely explanations than an "ageist" bias. Concerns about a higher risk of bleeding in older patients may restrict the use of invasive therapies, as bleeding has been shown to be an independent predictor of a poor outcome after an ACS event.[58]

People with diabetes

Diabetes is an important risk factor for cardiovascular disease, with a threefold increased risk of ACS, and an increased risk of post-infarct heart failure, recurrent ischaemia and death.[59] In Australia, 25% of patients who present with ACS have diabetes.[2] Compared with patients without diabetes, patients whose ACS occurs in the setting of diabetes tend to have more extensive coronary artery disease[60] and angioscopic evidence of more unstable disease with ulcerated plaques and intracoronary thrombi.[61] There is evidence of disordered cardiac function in diabetes which may be independent of myocardial ischaemia,[62] and includes a high prevalence of diastolic ventricular dysfunction.[63]

Patients with poor glycaemic control during their ACS have a worse outcome. Even modest elevations of plasma glucose levels in patients without known diabetes, previously referred to as "stress hyperglycaemia", is related to increased mortality.[64] While intensive medical therapy to achieve strict glycaemic control in patients with diabetes has been shown to reduce the risk of microvascular complications and some cardiovascular disease events in long-term follow-up,[65,66] there have been inconsistent results in the context of ACS. While small early open-label clinical studies appeared to have favourable results,[67] subsequent larger blinded randomised controlled trials failed to confirm any clear benefit of insulin- or sulfonylurea-based therapy to tightly control glucose levels.[68] The use of fixed-rate glucose, insulin and potassium (GIK) infusions has been studied in several trials, including the CREATE-ECLA study in patients with STEMI,[69] with prespecified analyses combined with the GIK component of the OASIS-6 trial.[70] These trials included more than 20 000 patients, 5000 of whom had diabetes. There was no beneficial effect of GIK infusion on outcomes, with possible harm resulting from excess fluid load, although the early excess in mortality became neutral at 30 days. When prehospital GIK therapy was administered to patients with suspected ACS, the IMMEDIATE trial demonstrated no initial benefit[71] or improvement in overall outcomes at 1 year.[72]

The role of intensive insulin therapy in ACS patients has been further informed by studies of strict glycaemic control in critically ill patients. The Australian NICE-SUGAR trial in multicentre intensive care settings demonstrated increased mortality with intensive glycaemic control and emphasised the serious adverse consequences of hypoglycaemia in these patients.[73] There was a lower mortality rate with a blood glucose target of below 10.0 mmol/L (< 180 mg/dL) than with a target of 4.4–6.1 mmol/L (81–108 mg/dL).[73] Current guidelines have recognised the differences between long-term benefits of intensive glycaemic control in younger patients with more recent diabetes onset, and the lack of benefit or potential harm among the critically ill or older patients with longstanding diabetes at the time of ACS.[74] The focus should be on active management of hyperglycaemia, with blood glucose levels below 11.0 mmol/L while avoiding hypoglycaemia. Dose-adjusted insulin infusions with regular monitoring of blood glucose levels should be considered, but routine administration of insulin and glucose with or without potassium is not recommended unless there is a clinical indication.

Trials of most guideline-indicated pharmacotherapy for patients with ACS and diabetes have demonstrated similar or greater risk reduction than for patients without diabetes. Dual antiplatelet therapy with aspirin and clopidogrel has demonstrated similar benefits for patients with diabetes compared with overall trial participants, although people with diabetes face a higher residual risk of recurrent events, possibly reflecting more persistent platelet activation. Prasugrel and ticagrelor offer more rapid and complete platelet inhibition and superior net clinical benefit to clopidogrel in studies of patients with diabetes and ACS, with similar overall bleeding rates in patients with diabetes.[75,76] Inhibitors of platelet glycoprotein IIb/IIIa receptors (including abciximab, eptifibatide and tirofiban) may have a role in high-risk ACS patients, including people with diabetes who are undergoing PCI.[77]

Statins have been shown to offer consistent benefit for secondary prevention of cardiovascular events among patients with diabetes, compared with placebo. The Cholesterol Treatment Trialists' analysis included more than 1000 participants with type 1 diabetes, mainly middle-aged people with prior cardiovascular disease, and found a similar risk reduction to that seen with type 2 diabetes.[78] Meta-analysis of trials examining more intensive versus moderate statin therapy have confirmed similar benefits for participants without diabetes.[79] For patients with diabetes and ACS, high-dose atorvastatin was superior to pravastatin, with a greater absolute risk reduction than was observed in patients without diabetes. It was noted that only 38% of participants with diabetes achieved the intended goals of a low-density lipoprotein

cholesterol level below 1.81 mmol/L (< 70 mg/dL) and a high-sensitivity C-reactive protein level below 2 mg/L.[80] Dyslipidaemia is common among people with diabetes, and has been recognised as an independent predictor of adverse outcomes. Trials to date have demonstrated the primary role of statins, but there is some evidence of benefit for fibrates in patients with diabetes and dyslipidaemia for long-term secondary prevention.[81,82]

For ACS, patients with diabetes compared with the overall population obtain similar or greater reduction in mortality and recurrent myocardial infarction with an early invasive strategy and revascularisation when possible.[83] The choice of revascularisation approach is complicated by superior results with coronary artery bypass graft (CABG) surgery compared with PCI in patients with diabetes and multivessel disease, even when new-generation drug-eluting stents are used.[84,85] These trials, however, did not typically include patients with ACS. The recommendations of the American College of Cardiology Foundation/American Heart Association guidelines are that for patients with diabetes, single-vessel disease in the setting of NSTEACS[86] or acute coronary occlusion of the infarct-related vessel in STEMI[87] should be managed with PCI, but CABG is preferred for the management of multivessel disease.

Aboriginal and Torres Strait Islander people

Coronary heart disease is twice as prevalent in the Australian Indigenous population as the non-Indigenous population.[88] This population has a high prevalence of cardiovascular risk factors[89] and established atherosclerosis.[90] A detailed 2006 report by the Australian Institute of Health and Welfare showed that Indigenous Australians had three times the rate of major coronary events and more than twice the inhospital coronary heart disease death rate of other Australians.[91] The high incidence affects remote-dwelling[92] and urban-dwelling Aboriginal Australians.[93,94] The disparities are even more striking in younger age groups. In a Western Australian study, the incidence of coronary events in the 25–29-years age group was 27 times (men) and 35 times (women) higher than in non-Aboriginal participants of the same age, decreasing to two to three times the non-Indigenous rates at 70–74 years.[95] A higher frequency of comorbid conditions, primarily diabetes, adversely affects short- as well as long-term survival.[96]

There are complex sociocultural barriers to delivery of optimal care for Indigenous patients with ACS.[97] Lower rates of treatment have been reported. The Australian Institute of Health and Welfare study of 2006[88] reported a 40% lower rate of being investigated by angiography, a 40% lower rate of coronary angioplasty or stent procedures and a 20% lower rate of CABG surgery. These apparently lower rates of coronary revascularisation in Aboriginal patients disappeared when patients were matched for age, sex and comorbidity. After this adjustment, the rates and type of intervention (including PCI and CABG surgery) during an ACS event were identical.[98] Similarly, the adjusted rates of evidence-based prescribing for post-hospital secondary prevention were similar in Aboriginal and non-Aboriginal patients.[99]

Conclusions

Some subgroups of patients experiencing ACS require special attention in assessment and management. While women, older people, people with diabetes and Indigenous patients may be underrepresented in clinical trials, there is evidence that most guideline-based therapies offer similar benefits in these subgroups. Barriers to routine prescription of effective post-ACS therapies in these patients need to be overcome.

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