

Reperfusion therapy in the acute management of ST-segment-elevation myocardial infarction in Australia: findings from the ACACIA registry

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During 2010, more than 47 000 hospitalisations for ST-segment-elevation myocardial infarction (STEMI) are expected in Australia.¹ Morbidity and mortality will be significant — at 12 months, 8.9% will have had a repeat myocardial infarction or stroke and 8% will have died.² The estimated economic cost of acute coronary syndromes (ACS) amounts to \$17.9 billion, comprising \$1.8 billion in direct hospital costs, \$3.8 billion indirect costs, and \$12.3 billion from loss in the value of health.¹ Fortunately, trial evidence suggests that expeditious and effective reperfusion reduces morbidity and mortality.³

There is a dearth of recent information on local delivery of this proven life-saving treatment in Australia.⁴⁻⁶ Without data and international comparisons, it is difficult to address issues of evidence implementation at the national level and to identify priorities for local action.⁷

In this article, we explore the Acute Coronary Syndrome Prospective Audit (ACACIA; protocol number PM_L_0051), describing the Australian care and outcomes of patients with STEMI. We analyse the acute management of STEMI, determining factors associated with delaying reperfusion or not reperfusing, and assess whether delayed reperfusion or non-reperfusion translates to poorer outcomes.

METHODS

The ACACIA registry was a nationwide prospective audit of ACS conducted between 1 November 2005 and 31 July 2007.⁸ The registry involved 39 remote, rural, and metropolitan hospitals across all states and territories of Australia. Hospitals were asked to enrol 100–150 consecutive patients presenting with suspected ACS. Larger hospitals were presumed to have shorter, and smaller hospitals longer, recruitment periods. Ethics committee approval was obtained from each site. Consent to access medical records was obtained from all patients. For patients who died

ABSTRACT

Objective: To describe the contemporary management and outcomes of patients presenting with ST-segment-elevation myocardial infarction (STEMI) in Australia.

Design, participants and setting: Observational analysis of data for patients who presented with suspected STEMI and enrolled in the Australian Acute Coronary Syndrome Prospective Audit from 1 November 2005 to 31 July 2007.

Main outcome measures: Factors associated with use of reperfusion therapy and timely use of reperfusion therapy, and the effects of reperfusion on mortality.

Results: In total, 755 patients had suspected STEMI. Median time to presentation was 105 minutes (IQR, 60–235 minutes). Reperfusion therapy was used in 66.9% of patients (505/755), and timely reperfusion therapy in 23.1% (174/755). Thrombolysis was administered in 39.2% of those who received reperfusion therapy (198/505), while 60.8% (307/505) received primary percutaneous intervention. Cardiac arrest (OR, 2.83; $P=0.001$) and treatment under the auspices of a cardiology unit (OR, 2.14; $P=0.02$) were associated with use of reperfusion therapy. A normal electrocardiogram on presentation (OR, 0.42; $P=0.01$), left bundle branch block (OR, 0.18; $P=0.001$), acute pulmonary oedema (OR, 0.34; $P<0.01$), history of diabetes (OR, 0.54; $P<0.01$), and previous lesion on angiogram of $>50\%$ (OR, 0.51; $P=0.001$) were associated with not using reperfusion. In-hospital mortality was 4.0% (30/755), mortality at 30 days was 4.8% (36/755), and mortality at 1 year was 7.8% (59/755). Receiving reperfusion therapy of any kind was associated with decreased 12-month mortality (hazard ratio [HR], 0.44; 95% CI, 0.25–0.78; $P<0.01$). Timely reperfusion was associated with a reduction in mortality of 78% (HR, 0.22; $P=0.04$). There were no significant differences in early and late mortality in rural patients compared with metropolitan patients ($P=0.66$).

Conclusion: Timely reperfusion, not the modality of reperfusion, was associated with significant outcome benefits. Australian use of timely or any reperfusion remains poor and incomplete.

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before giving consent, local ethics committees granted access to medical records.

Definition of ST-segment-elevation myocardial infarction

This analysis was restricted to patients admitted after a diagnosis of suspected STEMI. Patients presenting with symptoms suggestive of angina or angina-equivalent were included as having suspected STEMI if they had persistent ST-segment elevation >1 mm in two contiguous leads, or new or presumed new left bundle branch block (LBBB). Changes on electrocardiogram (ECG) were coded by the hospital where the ECG was taken and independently evalu-

ated by a trained clinician centrally. Discrepancies were adjudicated by a cardiologist.

Clinical variables

ACACIA focused on demographic, clinical procedural and logistical factors involved in the management of patients with ACS. In-hospital and 12-month outcomes were recorded. Late outcomes were documented by re-examining case notes, telephone interview, and examination of the National Death Index. Detailed descriptions of the clinical variables recorded have been previously published.⁸ Time to presentation was defined as time from symptom onset to first medical (doctor) contact. Time to reper-

fusion therapy was time from presentation until the time reperfusion therapy was administered, either by thrombolysis (door-to-needle), or primary percutaneous intervention (primary PCI; door-to-balloon). Reperfusion was considered timely if the patient received either thrombolysis within 30 minutes of presentation, or underwent angiography (and primary PCI if appropriate) within 90 minutes of presentation.⁹ Patients presenting to remote (17) and rural hospitals (114) were combined and referred to as "rural".

Statistical analysis

Factors showing a normal or Gaussian distribution are reported as means (\pm SD) and

those showing a non-Gaussian distribution are reported as medians (interquartile ranges [IQR]). Counts are presented as numbers and percentages. Comparisons between groups were carried out using χ^2 tests for binary factors and Kruskal–Wallis equality of populations rank test for continuous variables.

Baseline pretreatment factors that may be associated with non-reperfusion or delayed reperfusion were examined by stepwise forward logistic regression using robust estimates of variance allowing for intra-class correlation given the cluster design of the study. The factors examined included past history of: diabetes; hypertension; dyslipidaemia; smoking; family history of ischaemic heart disease; coronary artery disease;

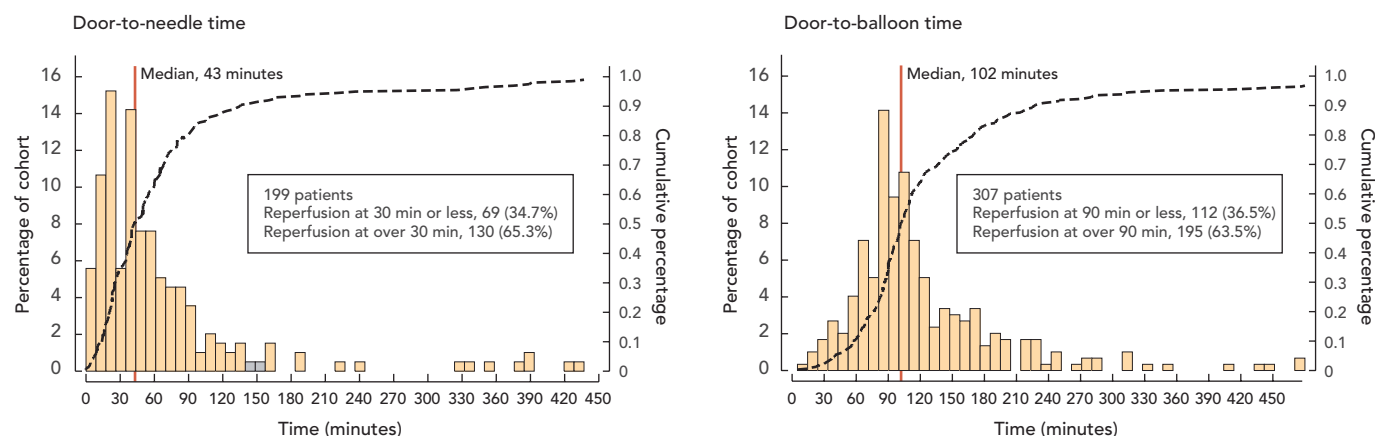
myocardial infarction (MI); obstructive sleep apnoea; malignancy; congestive cardiac failure; acute pulmonary oedema (APO) on presentation, previous angiography with >50% lesion; PCI; coronary artery bypass graft (CABG); cerebrovascular disease (CVA); peripheral vascular disease; and atrial fibrillation (AF). On presentation, we recorded: sex; age; systolic blood pressure; heart rate; Killip class \geq 2; shock; APO; calculated glomerular filtration rate; dialysis dependency; troponin positivity; creatine kinase level; white cell count; waist circumference; height; weight; smoking status; normal ECG; amount of ST deviation; region of ST change; LBBB; arrhythmia (and type); angina category; episodes of chest pain;

1 Demographic and clinical characteristics of the 755 patients enrolled in the ACACIA registry who had suspected ST-segment-elevation myocardial infarction at admission to participating metropolitan and rural hospitals

Characteristic	Metropolitan hospitals	Rural hospitals	All hospitals	P
Number of patients	624	131	755	
Mean age in years (SD)	62.27 (12.97)	62.12 (14.12)	62.25 (13.17)	0.85
Female	164 (26.3%)	31 (23.7%)	195 (25.8%)	0.53
Diabetes	111 (17.8%)	24 (18.3%)	135 (17.9%)	0.89
Hypertension	313 (50.2%)	62 (47.3%)	375 (49.7%)	0.56
Dyslipidaemia	288 (46.2%)	51 (38.9%)	339 (44.9%)	0.13
Current smoking	200 (32.1%)	48 (36.6%)	248 (32.9%)	0.30
Family history of coronary artery disease	214 (34.3%)	34 (26.0%)	248 (32.9%)	0.10
Prior myocardial infarction	86 (13.8%)	20 (15.3%)	106 (14.0%)	0.66
Prior angiogram with lesion > 50%	62 (9.9%)	5 (3.8%)	67 (8.9%)	0.03
Prior percutaneous coronary intervention	67 (10.7%)	13 (9.9%)	80 (10.6%)	0.78
Prior coronary artery bypass graft	22 (3.5%)	3 (2.3%)	25 (3.3%)	0.47
Prior stroke	20 (3.2%)	3 (2.3%)	23 (3.1%)	0.58
Known peripheral vascular disease	22 (3.5%)	3 (2.3%)	25 (3.3%)	0.47
Prior atrial fibrillation	26 (4.2%)	13 (9.9%)	39 (5.2%)	<0.01
Normal electrocardiogram on presentation	26 (4.2%)	4 (3.1%)	30 (4.0%)	0.55
Anterior STEMI on presentation	283 (45.4%)	53 (40.5%)	336 (44.5%)	0.31
Inferior STEMI on presentation	292 (46.8%)	74 (56.5%)	366 (48.5%)	0.04
New left bundle branch block on presentation	20 (3.2%)	3 (2.3%)	23 (3.1%)	0.58
Other STEMI on presentation	33 (5.3%)	3 (2.3%)	36 (4.8%)	0.14
Acute pulmonary oedema on presentation	26 (4.2%)	6 (4.6%)	32 (4.2%)	0.83
Cardiac arrest on presentation	50 (8.0%)	13 (9.9%)	63 (8.3%)	0.47
Median creatinine clearance in mL/min (IQR)	74.52 (62.13–88.26)	70.96 (53.85–86.01)	73.8 (60.62–87.89)	0.03
Management by specialist cardiology team	158 (25.3%)	11 (8.4%)	169 (22.4%)	<0.001
Median symptom onset to presentation in minutes (IQR)	106.5 (60–231)	91 (50–244)	105.0 (60–235)	0.30
Reperfusion	419 (67.2%)	85 (64.9%)	505 (66.9%)	0.62
Timely reperfusion	142 (22.8%)	32 (24.4%)	174 (23.1%)	0.68
Thrombolysis	135 (21.6%)	63 (48.1%)	198 (26.2%)	<0.001
Median door-to-needle time in minutes (IQR)	43 (23–73.5)	41 (22–85)	43.0 (23–75)	0.99
Primary percutaneous coronary intervention	284 (45.5%)	23 (17.6%)	307 (40.7%)	<0.001
Median door-to-balloon time in minutes (IQR)	101 (83.5–148.5)	121 (79–172)	102.0 (83–155)	0.34

STEMI = ST-segment-elevation myocardial infarction. ACACIA = Australian Acute Coronary Syndrome Prospective Audit. IQR = interquartile range. ◆

2 Door-to-needle and door-to-balloon times for the patients treated with reperfusion therapy



cardiac arrest; rural status of the hospital where the patient presented; distance of nearest referral hospital (if transferred); academic/non-academic hospital; private/public hospital; hospital catchment population; hospital coronary care beds; number of ACS presentations per year to hospital; number of catheterisation laboratories; availability of PCI facilities; level of first medical officer contact; cardiology unit availability; and treating unit specialty. A significance level of 0.05 was used for addition to the model.

Cox proportional hazards models accounting for the cluster design were used to determine outcomes by the type of reperfusion therapy and timeliness of reperfusion. Each model adjusted for individual calculated Global Registry of Acute Coronary Events (GRACE) risk score and factors significantly associated with use of reperfusion to adjust for baseline risk.¹⁰ Kaplan–Meier survival curves were plotted for use and timeliness of reperfusion. Statistical analysis was performed using Stata 11.0 (StataCorp, College Station, Tex, USA).

RESULTS

A total of 3402 patients were enrolled in the ACACIA registry, of whom 755 met the criteria of suspected STEMI at admission. Of these 755 patients, 707 (93.6%) were discharged with a final diagnosis of STEMI. Further, 684 patients (90.6%) presented within 12 hours of symptom onset. Demographic and clinical characteristics of the study cohort according to rural or metropolitan region are shown in Box 1. Overall, there were few differences between baseline characteristics of metropolitan and rural patient groups.

Use of reperfusion therapy

Most of the 755 patients (505; 66.9%) were treated with some form of reperfusion therapy. Thrombolysis was administered in 198 of these 505 patients (39.2%), while 307 (60.8%) received primary PCI. One patient was treated with both thrombolysis and PCI.

The magnitude of ST-segment elevation may influence management. Of the 65 patients with the lowest levels of diagnostic ST-segment elevation at presentation (1–2 mm in two adjacent precardial leads), 52 (80.0%) had a final diagnosis of STEMI, although only 17 (26.2%) were treated with some form of reperfusion therapy.

Of the 85 rural patients who were treated with reperfusion therapy, 63 (74.1%) received thrombolysis. In the metropolitan group of 419 patients treated with reperfusion therapy, 135 (32.2%) received thrombolysis and the remaining 284 (67.8%) received primary PCI.

Timing of reperfusion therapy

Door-to-needle and door-to-balloon times are detailed in Box 1 and Box 2. Timely reperfusion was achieved in 23.1% of the

total population (174 patients), representing 34.5% of the 505 who were treated with any form of reperfusion therapy. For those treated with reperfusion therapy, there was no difference in the likelihood of timely reperfusion between rural and metropolitan patients for either the provision of primary PCI (7 of 23 rural patients [30.4%] v 98 of 284 metropolitan patients [34.5%]; $P=0.69$) or thrombolysis (26 of 63 rural patients [41.3%] v 44 of 135 metropolitan patients [32.6%]; $P=0.23$). Overall, angiography was performed on 671 of 755 patients (88.9%) during the initial admission; however, metropolitan patients were more likely than rural patients to receive angiography (575 of 624 metropolitan patients [92.2%] v 96 of 131 rural patients [73.3%]; $P<0.001$). Stepwise forward logistic regression clustered by hospital site revealed the factors that were associated with use of reperfusion therapy, and the adjusted odds ratios for these factors are shown in Box 3. Box 4 shows the adjusted odds ratios for factors associated with timely reperfusion therapy for those who were treated with reperfusion.

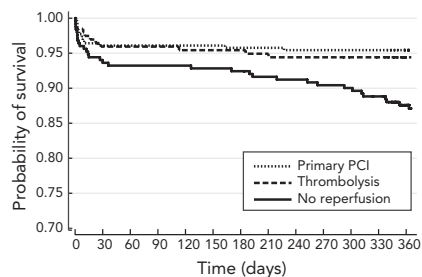
3 Factors associated with use of reperfusion therapy

Factor	Odds ratio	P	95% CI
Cardiac arrest on presentation	2.83	0.001	1.55–5.17
Cardiology team v non-cardiology team	2.14	0.02	1.11–4.12
New left bundle branch block on presentation	0.18	0.001	0.065–0.51
Acute pulmonary oedema on presentation	0.34	<0.01	0.17–0.70
Normal electrocardiogram on presentation	0.42	0.01	0.21–0.82
Diabetes	0.54	<0.01	0.36–0.81
Previous > 50% lesion on angiogram	0.51	0.001	0.34–0.76

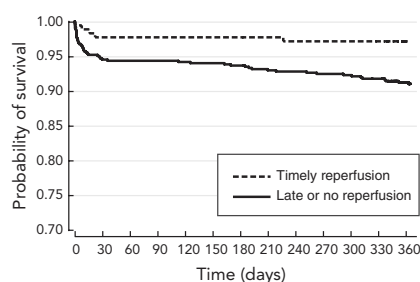
4 Factors associated with timely reperfusion therapy

Factor	Odds ratio	P	95% CI
Arrhythmia on presentation	1.96	0.001	1.30–2.96
Chronic obstructive airways disease	0.10	0.02	0.01–0.71
Previous myocardial infarction	0.36	<0.001	0.20–0.63
Delayed time to presentation (for each hour)	0.88	<0.01	0.81–0.96
More than one episode of chest pain	0.53	<0.01	0.34–0.83

5 Kaplan–Meier survival estimates, by type of reperfusion



6 Kaplan–Meier survival estimates, by timeliness of reperfusion



Early and late outcomes

Overall, the rate of death was 4.0% (30 of the total 755 patients) during the index hospital admission, 4.8% (36 of 755) at 30 days, and 7.8% (59 of 755) at 12 months. Recurrent MI occurred in 2.4% of patients (18 of 755) during the hospital admission, with no other events at 30 days, but increased to 6.8% of patients (51 of 755) by 12 months. The stroke rate was 0.7% (5 of 755) during admission, with no other reported events at 12-month follow-up. The combined rate of death, MI, and stroke at 30 days and 12 months was 9.4% (71 of 755 patients) and 13.9% (105 of 755 patients), respectively. These outcomes did not differ significantly between metropolitan and rural regions ($P=0.66$).

Mortality by reperfusion therapy

After adjusting for baseline risk using the GRACE score and adjusting for potential confounders, reperfusion of any kind was associated with a reduction in mortality throughout 12 months of follow-up (hazard ratio [HR], 0.44; 95% CI, 0.25–0.78; $P<0.01$). This benefit remained evident for primary PCI compared individually with those receiving no reperfusion therapy (HR, 0.33; 95% CI, 0.18–0.61; $P<0.001$), but not for thrombolysis (HR, 0.66; 95% CI, 0.26–1.68; $P=0.38$; Box 5).

Outcome by timeliness of reperfusion

Timely reperfusion, compared with late or no reperfusion, was associated with a

decrease in the odds of death throughout the 12-month follow-up period of 78.3% (HR, 0.22; 95% CI, 0.05–0.95; $P=0.04$), even after adjustment by baseline GRACE score (Box 6). The difference in the combined rate of death, recurrent MI, and stroke throughout the 12 months did not reach statistical significance (HR, 0.66; 95% CI, 0.36–1.20, $P=0.17$).

DISCUSSION

In this study, we describe the contemporary Australian experience of reperfusion therapy in patients with STEMI, and detail the associations and outcomes related to the use and timeliness of both thrombolysis and primary PCI.

First, we have again observed the benefits of reperfusion therapy, which have previously been demonstrated in various randomised controlled trials and registries. Although there have been no randomised trials comparing any reperfusion therapy to no reperfusion therapy, it is known that 30-day mortality rates for medical treatment alone are around 13%, compared with 6%–7% for optimal thrombolytic therapy.^{11,12} Previous randomised controlled trial mortality rates were 3%–5% for optimal primary PCI.^{13,14} Of note, these results were from clinical trials where patient selection resulted in a lower overall risk profile. Our contemporary Australian 30-day mortality rate of 4.8% (36 of 755 patients) among those receiving reperfusion therapy is congruent with clinical trial mortality rates.

When the modes of reperfusion are compared, mortality benefits persisted for primary PCI but not for thrombolysis. This is likely due to the small sample size, but is consistent with clinical trials demonstrating decreased mortality with primary PCI versus thrombolysis.¹⁵

Our second important finding relates to the contemporary patterns of use of reperfusion therapy in Australia. Although all patients in our cohort were suspected of presenting with STEMI on admission and 93.6% were discharged with a final diagnosis of STEMI, only 66.9% received any form of reperfusion therapy. This is despite a median time to presentation of only 105 minutes, and 90.6% of patients presenting within 12 hours of symptom onset. The fact that these rates are similar to those documented by various registries, with no improvement over the past two decades, is of concern.^{16,17} The GRACE registry (reporting on 1763 patients presenting with STEMI within 12 hours of symptom onset in 94 hospitals from 14 countries) found that 30% of eligible patients with STEMI did not receive reperfusion therapy.¹⁸ Therefore, despite the existence of guidelines, their implementation remains a challenge, and this evidence suggests that there is an ongoing need for strategies that facilitate this implementation.

Third, our study reconfirms, in a routine clinical practice setting, the advantages of early reperfusion. Contrasting rural and metropolitan populations reiterates this point. When these two groups were compared, there was no difference in long-term outcomes. Although the rates of reperfusion were similar in both groups, the rural group achieved that rate mainly through thrombolysis, while the metropolitan group achieved a similar rate from PCI. This underscores that time to reperfusion is more important than the modality of reperfusion. In this sense, our findings support current guideline recommendations.⁹ The Australian guidelines are slightly more specific than those of the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on this point,³ in that while patients presenting with STEMI should be considered for primary PCI if the time from first medical contact to balloon time is less than 90 minutes, an estimated time delay beyond 90 minutes should lead thrombolysis to be considered as the primary treatment.

A recent consensus recommendation from the National Heart Foundation for

translating knowledge into action in ACS outlined specific recommendations and actions for early reperfusion for STEMI.¹⁹ These included empowering and supporting appropriately trained health care workers to initiate thrombolysis in regional and remote settings, to set up protocols for single-call activation of PCI systems that operate 24 hours a day, 7 days a week, and to optimise the use of existing infrastructure for reperfusion through regional collaborations and protocols. Each recommendation is backed by sound evidence,^{20,21} and early initiatives both in Australia^{22,23} and elsewhere have shown quantifiable outcome improvements.²⁴

Various ST-segment criteria have been proposed for reperfusion therapy.²⁵ Current Australian guidelines reflect the Minnesota Code and previous trials of thrombolysis, which classified STEMI as persistent ST-segment elevation ≥ 1 mm in two contiguous limb leads or ≥ 2 mm in two contiguous chest leads (or presumed new LBBB).^{26,27} Some more recent trials of thrombolysis and PCI have used ≥ 1 mm in any two contiguous leads, while the 2007 consensus document of the European Society of Cardiology, the ACC, the AHA and the World Heart Federation on the universal definition of myocardial infarction uses the Minnesota Code definition for men and changes the criteria for praecordial leads in women to ≥ 1.5 mm.²⁸⁻³⁰ In our study, 8.6% of all patients with suspected STEMI on admission had praecordial ST-segment elevation of 1–2 mm. Of these, 80% went on to have a discharge diagnosis of STEMI, and may therefore have benefitted from reperfusion therapy, which was only used in 26.2% of this group. A strategy of urgent coronary angiography with intervention when required in such patients with “borderline” ST-segment elevation may improve the rate of reperfusion in this group. In hospitals without PCI facilities, patients in this subgroup who are not considered candidates for thrombolysis initially may require close monitoring for progressive ECG changes or may need to be considered for transfer to a PCI-capable hospital where feasible.

Finally, we demonstrated factors associated with not using or delaying reperfusion therapy. Our findings add to the existing factors identified in other Australian cohort studies that included older age (≥ 70 years), past stroke, and past hypertension, and reinforces other factors such as diabetes and past ACS.³¹ Similarly, it was observed that more patient complexity was associated

with less reperfusion. This is not surprising, given the greater uncertainty with respect to relative weighing of risk and benefit. Objective estimates of risk and benefit provided through decision support may help to improve outcomes.

Factors associated with not using reperfusion therapy are the same factors associated with greatest benefit from reperfusion. For example, patients who present with normal electrocardiograms and develop ST-segment elevation in hospital are often those who present very early in the course of their acute syndrome, which represents a “window of opportunity” in which a threatened STEMI may be treated before myocardial damage becomes irreversible.³² Similarly, among patients presenting with acute pulmonary oedema, data from both the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial³³ and the Duke registry³⁴ suggest that these patients experience better inpatient and long-term outcomes when the infarct-related artery is reopened, either by thrombolysis or PCI. Although numbers in our study were small, about 70% of patients with LBBB on presentation were not reperfused despite an undisputed indication for therapy (in the presence of typical chest pain), representing one clear area where improvements in care may be made.

Treating unit specialty appeared to have an impact on use of reperfusion therapy. Similar findings have been previously reported with referral for coronary angiography.³⁵ This finding has implications for rural regions, where access to specialist cardiac services are limited, and argues for widespread adaptation of clinical decision support systems,³⁶ as well as specialist clinical networks in cardiology.³⁷⁻³⁹

The main limitation of our study was that it was observational by design. As such, it is suboptimal for estimating treatment effects. However, the data were not used to estimate new treatment effects, but simply to confirm previously robust clinical trial results. A second limitation was the limited representation of rural and remote patients. Census data indicate that roughly 14% of Australians live in rural and remote regions.⁴⁰ Although these patients represented 17.4% of our cohort, this sample was derived from a few select centres. It is clear that future registries will need to focus more on country patients, and that data infrastructure should match clinical infrastructure.

This study documents the clear benefit of early reperfusion therapy, yet highlights the

discordance between trial evidence, guideline recommendations, and actual practice. Our findings provide a strong case for continued audit and possible system redesign of our ACS management through a nationwide ongoing clinical registry.

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COMPETING INTERESTS

Luan Huynh, Derek Chew and David Brieger have in the past received modest speaker fees and travel assistance to attend academic meetings from Sanofi-aventis and its competitors. Sanofi-aventis had a representative on the steering committee and was given 30 days to review the article, but did not make any changes.

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