Differences in management and outcomes for men and women with ST-elevation myocardial infarction

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The known Sex differences in the management and outcomes of patients with acute coronary syndromes have been reported, but many reported analyses were not adjusted for confounding covariates.

The new Despite broader awareness of STEMI protocols, revascularisation rates for women with STEMI are lower than for men. In hospital, rates of major adverse cardiovascular events and mortality were similar, but at 6 months were significantly higher for women. Women were less frequently referred for cardiac rehabilitation or prescribed preventive medications on discharge.

The implications Clinicians should consider potential barriers to equity for women in the management of STEMI.

Abstract

Objective: To examine whether there are sex differences in the characteristics, management, and clinical outcomes of patients with an ST-elevation myocardial infarction (STEMI).

Design, setting: Cohort study; analysis of data collected prospectively by the CONCORDANCE acute coronary syndrome registry from 41 Australian hospitals between February 2009 and May 2016.

Participants: 2898 patients (2183 men, 715 women) with STEMI.

Main outcome measures: Rates of revascularisation (percutaneous coronary intervention [PCI], thrombolysis, coronary artery bypass grafting [CABG]), adjusted for GRACE risk score quartile. Secondary outcomes: timely vascularisation rates; major adverse cardiac event rates; clinical outcomes and preventive treatments at discharge.

Results: The mean age of women with STEMI at presentation was 66.6 years (SD, 14.5 years), of men, 60.5 years (SD, 12.5 years). The proportions of women with hypertension, diabetes, prior stroke, chronic kidney disease, chronic heart failure, or dementia were larger than those of men; fewer women had histories of previous coronary artery disease or myocardial infarction, or of prior PCI or CABG. Women were less likely to have undergone coronary angiography (odds ratio, adjusted for GRACE score quartile [aOR], 0.53; 95% CI, 0.41–0.69) or revascularisation (aOR, 0.42; 95% CI, 0.34–0.52); they were less likely to have received timely revascularisation (aOR, 0.72; 95% CI, 0.63–0.83) or primary PCI (aOR, 0.76; 95% CI, 0.61–0.95). Six months after admission, the rates of major adverse cardiovascular events (aOR, 2.68; 95% CI, 1.76–4.09) and mortality (aOR, 2.17; 95% CI, 1.24–3.80) were higher for women. At discharge, significantly fewer women than men received β-blockers, statins, and referrals to cardiac rehabilitation.

Conclusion: Women with STEMI are less likely to receive invasive management, revascularisation, or preventive medication at discharge. The reasons for these persistent differences in care require investigation.

Cardiovascular disease is the leading cause of morbidity and mortality in both sexes, but an extensive literature has described differences between men and women in clinical presentation and pathophysiology that may influence management and outcomes.[1,2] Observational studies have found that women with acute coronary syndromes (ACS) more frequently present with atypical symptoms,[3] with more comorbidities,[4] and at an older age, and that plaque rupture[5] and high risk features[3,6,7] are less likely to be identified during angiography than in men.

Large hospital registry studies have found that women with ACS are less likely to receive evidence-based management, including coronary angiography and appropriate medications in hospital and at discharge.[4,6,8-10] Australian data similarly indicate that women with ACS are underinvestigated and that evidence-based therapies are less often prescribed than for male patients.[10-12]

Some studies have found that the higher mortality rates for women than for men with ACS in hospital,[4,6,9,10,13] at 30 days,[7,14] and at 6 months[3,13] are attenuated after adjusting for age and comorbid conditions, but others have found that differences persist despite adjustment.[8]

In our investigation, we wanted to avoid confounding by the significant interactions between sex and type of ACS identified in earlier studies.[7,14] We therefore focused on patients with STEMI, as the clinical presentation and diagnosis of this condition is relatively consistent and the patients receive a largely standardised management plan. We hypothesised that management and outcomes for men and women with STEMI should be similar after adjusting for risk level.

Our specific aims were to identify sex differences in the characteristics and outcomes of patients presenting with STEMI; to examine associations between sex and outcomes (morbidity and mortality) after adjusting for relevant covariates; and to explore whether there with differences in the prescribing of preventive medications for men and women after STEMI.

Methods

We analysed data from the CONCORDANCE (Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events) registry, an ongoing prospective ACS registry

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involving 41 sites around Australia that has enrolled patients since February 2009. The cohort for the current analysis was enrolled between February 2009 and May 2016. Details of the design and rationale of CONCORDANCE have been published elsewhere,[15] and are described only briefly here.

Setting and participants

Hospitals from all Australian states and territories participated. Twenty-eight hospitals (68%) are in metropolitan regions, 13 in rural locations; 30 (73%) have onsite cardiac catheterisation laboratories. All ACS patients can be enrolled, but most hospitals select a representative sample, usually enrolling the first ten adult patients (at least 18 years of age) admitted with suspected ACS each calendar month. An opt-out consent process was applied and consent waiver approved for patients who died or were too ill to provide consent.[15] Patients included in the analysis reported in this article were those with a final discharge diagnosis of STEMI.

Data collection

Patient characteristics, treatments and medical history at presentation, initial assessment and management, in-hospital investigations and management, and in-hospital morbidity and mortality are collected in a standardised electronic case report form. To ensure data quality, a random sample of submitted case report forms was audited. Patients undergoing percutaneous coronary intervention (PCI) were categorised as receiving either "primary PCI" or "other PCI". The Global Registry of Acute Coronary Events (GRACE) risk score was calculated for all patients. The GRACE risk score is a validated clinical risk prediction tool for estimating the cumulative 6-month risks of death and of death or myocardial infarction on the basis of eight factors: age, pulse rate, Killip class, systolic blood pressure, initial serum creatinine level, initial cardiac enzyme levels, cardiac arrest at admission, and ST segment deviation.[16]

The primary outcome was total revascularisation, a composite endpoint encompassing patients receiving PCI, thrombolysis, or coronary artery bypass grafting (CABG) during the index admission. We chose this outcome because delay in diagnosis or treatment is often cited as a cause of sex differences. Total revascularisation better captures whether the principal goal of revascularisation therapy was achieved in STEMI patients than assessing the rates of individual therapies.

Important secondary outcomes were also assessed:

- the components of the primary outcome: any PCI, primary PCI, thrombolysis, CABG;
- timely revascularisation, defined as patients presenting to hospital within 12 hours of symptom onset receiving primary PCI with a door-to-balloon time of no more than 90 minutes or thrombolysis with a door-to-needle time of no more than 30 minutes;
- major adverse cardiac events, a composite endpoint including myocardial re-infarction, and stroke or death with a cardiac cause;
- mortality in hospital and within 6 months of admission.

In patients discharged alive, we also examined discharge medications and referral to cardiac rehabilitation.

Statistical analysis

Simple group comparisons employed χ^2 tests for categorical variables and Student t tests for continuous variables, adjusted for clustering. For categorical univariate analysis of outcomes with more than two levels, we used the Rao–Scott χ^2 test. $P < 0.05$ was deemed statistically significant.

We compared clinical characteristics and outcomes for men and women. Associations between sex and each outcome were examined in univariate and multivariate logistic regression models using the generalised estimation equation framework. Multivariate models, adjusted for the GRACE risk score (categorised as quartiles), were calculated for each of the outcomes: revascularisation, discharge medication, cardiac rehabilitation referral, mortality. In each model, we tested for interactions between each variable and sex, and adjusted for clustering. Several sensitivity analyses were undertaken: adjusting for time to presentation (defined as time between symptom onset and time of presentation to first hospital) as well as GRACE risk score for revascularisation therapies and clinical outcomes; comparing the primary outcome stratified by GRACE risk score or by year of index admission; restricting analyses of revascularisation therapies to hospitals able to perform PCI; restricting analysis of primary PCI rates to patients with significant coronary artery disease. All analyses were performed in SAS University Edition (SAS Institute).

Ethics approval

The study was approved by the Sydney Local Health District Human Research Ethics Committee (reference, CH62/6/2008-141). The CONCORDANCE registry was approved by the research and ethics committees at all participating sites.

Results

Of 10 656 people enrolled in the CONCORDANCE registry at 31 May 2016, 2898 (27.5%) had a final diagnosis of STEMI; 2183 (75.3%) were men, 715 (24.7%) women. In-hospital clinical outcome data were complete for all patients, and also for 2075 of 2627 patients (79.0%) eligible for follow-up at 6 months. GRACE risk scores could be calculated for 2790 of 2898 patients (96.3%) (2103 of 2183 men; 687 of 715 women). The mean age of women with STEMI at presentation was higher (66.6 years; standard deviation [SD], 14.5 years; men, 60.5 years; SD, 12.5 years), as was their mean GRACE score (123.5; SD, 33.3; men, 111.4; SD 30.0). Further, a larger proportion of women than of men had hypertension, diabetes, a history of prior stroke, chronic kidney disease, chronic heart failure, or dementia; fewer had a history of previous coronary artery disease or myocardial infarction, or of prior PCI or CABG (Box 1).

Women with STEMI were less likely to have undergone coronary angiography (odds ratio, adjusted for GRACE score quartile [aOR], 0.53; 95% confidence interval [CI], 0.41–0.69) or received revascularisation (aOR, 0.42; 95% CI, 0.34–0.52); they were less likely to have received timely revascularisation (aOR, 0.72; 95% CI, 0.63–0.83) or primary PCI (aOR, 0.76; 95% CI, 0.61–0.95). Rates of thrombolysis were similar for men and women, but in the subset of cases with data on timeliness, the maximum door-to-needle time of 30 minutes was less often met for women than men (29% *v* 37%); there was no difference in door-to-balloon times for primary PCI (50% *v* 52%) (Box 2). Overall rates of total revascularisation for both men and women improved during 2010–2015, but there was still a significant sex difference (online Appendix, table 1).

Women had higher rates of non-significant coronary artery disease (12.1% *v* 3.7%) and lower rates of two-vessel disease (24.7% *v*

1 Baseline characteristics of men and women with ST-elevation myocardial infarction enrolled in the CONCORDANCE registry, February 2009 – May 2016

	Men	Women
Total number	2183	715
Age (years), mean (SD)	60.5 (12.5)	66.6 (14.5)
Aboriginal or Torres Strait Islander	115 (5.3%)	51 (7.1%)
Hypertension	1035* (47.5%)	418† (58.8%)
Diabetes	412 (18.9%)	184 (25.7%)
Dyslipidaemia	931‡ (42.8%)	313§ (43.8%)
Smoking status		
Current	871¶ (40.1%)	268† (37.7%)
Ex-smoker	647¶ (29.8%)	129 (18.1%)
Never smoker	657¶ (30.2%)	314† (44.2%)
Peripheral artery disease	79 (3.6%)	30 (4.2%)
Prior myocardial infarction	335 (15.4%)	87 (12.2%)
Previous coronary artery disease	361 (16.5%)	80 (11.2%)
Previous percutaneous coronary intervention	249 (11.4%)	53 (7.4%)
Prior coronary artery bypass grafting	73 (3.3%)	11 (1.5%)
Prior heart failure	56 (2.6%)	31 (4.3%)
Previous atrial fibrillation	97 (4.4%)	43 (6.0%)
Prior stroke	85 (3.9%)	51 (7.1%)
Prior major bleeding	24 (1.1%)	8 (1.1%)
Dementia	42 (1.9%)	25 (3.5%)
Chronic kidney disease	86 (3.9%)	43 (6.0%)
Time to presentation (min), median (IQR)	104 (60–244)	120 (68–305)
Killip class		
I	1995 (91.4%)	606 (84.8%)
II	132 (6.1%)	76 (10.6%)
III	27 (1.2%)	21 (2.9%)
IV	29 (1.3%)	12 (1.7%)
GRACE score, mean (SD)	111.4 (30.0)	123.5 (33.3)

IQR = interquartile range; SD = standard deviation. Missing data: * five participants; † four participants; ‡ seven participants; § one participant; ¶ eight participants. ◆

29.7%) than men, but similar rates of single- and three-vessel coronary artery disease and of anterior STEMI (women, 51.0%; men, 51.8%) detected by coronary angiography (online Appendix, figure 1).

All sensitivity analyses yielded similar results to the main analysis, including after adjusting for time to presentation as well as for GRACE risk score (online Appendix, table 2), stratifying by GRACE risk score quartile (online Appendix, table 3), and restricting analysis to hospitals that were PCI-capable (online Appendix, table 4). In the analysis restricted to patients with significant coronary artery disease, the total revascularisation rate for women was lower than for men with STEMI (90.0% *v* 95.1%).

In hospital, women were more likely to have second or third degree atrioventricular block (aOR, 1.80; 95% CI, 1.08–3.00), and less likely to experience in-hospital cardiac arrest (aOR, 0.70; 95% CI, 0.51–0.96) or sustained ventricular tachycardia (aOR, 0.47; 95% CI, 0.26–0.83). Rates of in-hospital major adverse cardiac events and mortality were higher for women, but the differences were not statistically significant after adjusting for GRACE risk score quartile; however, at 6 months their major adverse cardiac event rate (aOR, 2.68; 95% CI, 1.76–4.09) and mortality (aOR, 2.17; 95% CI, 1.24–3.80) were higher than for men after adjusting for GRACE risk score quartile (Box 3). These differences in clinical outcomes were similar after adjusting for time to presentation as well as for GRACE score quartile (online Appendix, table 5).

At discharge, significantly lower proportions of women than of men received β-blockers, statins, and referrals to cardiac rehabilitation, but there were no sex differences for receiving second antiplatelet agents, aspirin, or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (Box 4).

Discussion

In our analysis of Australian ACS registry data, we found that the mean age of women presenting to hospital with STEMI was higher than for male patients, as was their mean GRACE risk score. Nevertheless, smaller proportions of women than men with STEMI had undergone coronary angiography or revascularisation; 6 months after admission, they were more likely to have had a major adverse cardiac event, and their mortality rate was higher. The lower overall revascularisation rate in women was explained by lower rates of primary PCI and CABG, as there was no sex difference for thrombolysis. These differences persisted even after adjusting for both time to presentation GRACE risk score quartile, in analyses restricted to patients with significant obstructive coronary artery disease, and in analyses restricted to PCI-capable hospitals. Our findings of lower rates of revascularisation of women than of men with STEMI are consistent with those of an analysis of Victorian ACS registry data; mortality in the Victorian study, however, was similar for men and women.[11,12] Further, women with STEMI in our study were less likely to receive some elements of secondary preventive treatment, including β-blockers and statins, and referral to cardiac rehabilitation.

The characteristics of the patients in our study are comparable with those of other Australian and international studies that have found that women present with ACS later in life than men, and have more comorbid conditions, especially diabetes and hypertension;[3,4,8,9,11,13,17-21] several of these studies also found that women were less likely to undergo invasive coronary angiography and revascularisation.[4,9,11,13,17,18] Three studies have reported rates of primary PCI in patients with STEMI. Registry data analyses in Switzerland (12 146 patients) and France (3510 patients) each found that primary PCI rates were lower for women than men with STEMI (30.9% *v* 40.3% and 47% *v* 55% respectively).[4,21] The lower rates of primary PCI in the Swiss registry (AMIS) study than in ours (women, 42.8%; men, 52.3%) are probably explained by the period of enrolment (AMIS, 1997–2006; CONCORDANCE, since 2009). A study by the Malaysian National Cardiovascular Disease–Acute Coronary Syndrome Registry (6378 patients) found much lower rates of primary PCI (women, 6.2%; men, 6.7%), and the rates of thrombolysis were also lower for women (64.4%; men, 74.6%).[9] It is not clear whether these differences in management are associated with poorer clinical outcomes for women; some registries from middle (upper and lower) and high income countries have found no sex difference in adjusted rates of in-hospital mortality.[4,9,13,17,18] An analysis of data in the Global Registry of Acute

2 Revascularisation therapies for patients with ST-elevation myocardial infarction, by sex

Revascularisation therapy	Men	Women	Adjusted odds ratio* (95% CI)	*P*
Number of patients	2183	715		
Coronary angiography	2088 (95.7%)	637 (89.1%)	0.53 (0.41–0.69)	< 0.001
Total revascularisation†	2001 (91.7%)	565 (79.0%)	0.42 (0.34–0.52)	< 0.001
Timely revascularisation‡	821/1943 (42.3%)	211/623 (33.9%)	0.72 (0.63–0.83)	< 0.001
Percutaneous coronary intervention (PCI)	1699 (77.8%)	465 (65.0%)	0.63 (0.52–0.75)	< 0.001
Primary PCI	1142 (52.3%)	306 (42.8%)	0.76 (0.61–0.95)	0.015
Other PCI	554 (25.4%)	159 (22.2%)	0.88 (0.68–1.14)	0.34
Door-to-balloon time ≤ 90 minutes§	537/1035 (51.9%)	136/272 (50.0%)	—	
Thrombolysis	704 (32.3%)	225 (31.5%)	0.99 (0.83–1.19)	0.93
Door-to-needle time ≤ 30 minutes§	213/570 (37.4%)	51/176 (29%)	—	
Coronary artery bypass graft (CABG)	163 (7.5%)	25 (3.5%)	0.42 (0.28–0.65)	< 0.001

CI = confidence interval. * Women *v* men; adjusted for GRACE risk score quartile. † Composite endpoint: patients receiving PCI, thrombolysis or coronary artery bypass, or CABG during the index admission. ‡ Primary PCI: maximum door-to-balloon time, 90 minutes; thrombolysis: maximum door-to-needle time, 30 minutes (each in patients presenting within 12 hours of symptom onset). § This could only be calculated for patients with complete data on arrival and ballooning or needle time. ◆

Coronary Events (14 Western countries; 26 755 patients) found higher adjusted 6-month major adverse cardiac event rates, but not higher mortality among women than men.[3]

The reasons for the persisting differences in the investigation and management of men and women in Australian hospitals are perplexing. By restricting our analyses to patients with STEMI, we minimised the effects of differences in management caused by type of ACS and level of risk. We found that women with STEMI in every GRACE risk score quartile received less comprehensive assessment and treatment. Current guidelines support invasive management of patients at high risk, while acknowledging that this increases the risk of complications.[22] Undertreatment of patients with a high risk score has been a consistent feature of ACS management in several studies.[23] Undertreatment in the population we examined might be caused by poor awareness that women with STEMI are generally at higher risk, or by a preference for subjectively determining risk rather than applying more reliable, objective risk prediction tools.[24]

The similar rates of in-hospital mortality in our study may reflect insufficient statistical power for detecting a sex difference at this time point. Differences in revascularisation rates in hospital may underlie the statistically significant differences in major adverse cardiac event rate and mortality at 6 months.

Treatment protocols for patients with STEMI have improved in Australia, and we found that overall rates of total revascularisation

3 Adverse events, in hospital and at 6 months, in patients with ST-elevation myocardial infarction, by sex

Inpatient event*	Men	Women	Adjusted odds ratio† (95% CI)	*P*
Total number of patients	2183	715		
Sustained ventricular tachycardia	81/2167 (3.7%)	16/712 (2.3%)	0.47 (0.26–0.83)	0.010
Cardiac arrest or ventricular fibrillation	156/2172 (7.2%)	51/712 (7.2%)	0.70 (0.51–0.96)	0.026
Atrial fibrillation/flutter	193/2168 (8.9%)	79/712 (11.1%)	0.91 (0.69–1.19)	0.46
Cardiogenic shock	130/2161 (6.0%)	57/712 (8.0%)	0.91 (0.69–1.21)	0.53
Major bleeding	178/2183 (8.2%)	71/715 (9.9%)	1.00 (0.74–1.34)	0.98
Myocardial infarction or re-infarction	67/2156 (3.1%)	24/709 (3.4%)	1.01 (0.69–1.47)	0.96
Acute renal failure	133/2165 (6.1%)	64/711 (9.0%)	1.08 (0.77–1.52)	0.65
Congestive heart failure	190/2154 (8.8%)	95/707 (13.4%)	1.19 (0.87–1.61)	0.28
Stroke	19/2160 (0.9%)	11/711 (1.6%)	1.62 (0.74–3.56)	0.23
Second or third degree atrioventricular block	32/2171 (1.5%)	20/712 (2.8%)	1.80 (1.08–3.00)	0.024
Major adverse cardiac events,‡ in-hospital	265/2183 (12.1%)	121/715 (16.9%)	1.15 (0.90–1.47)	0.27
Major adverse cardiac events,‡ at 6 months	61/1587 (3.8%)	59/508 (11.6%)	2.68 (1.76–4.09)	< 0.001
Mortality, in-hospital	116/2178 (5.3%)	64/712 (9.0%)	1.11 (0.74–1.66)	0.62
Mortality, at 6 months	35/1581 (2.2%)	32/506 (6.3%)	2.17 (1.24–3.80)	0.006

CI = confidence interval. * Recorded during the index admission unless otherwise stated. † Women *v* men; adjusted for GRACE risk score quartile. ‡ Myocardial re-infarction, stroke, or death from cardiac cause. ◆

4 Medications at discharge prescribed for patients with ST-elevation myocardial infarction, by sex

Medication	Men	Women	Adjusted odds ratio* (95% CI)	*P*
Total number of patients	2062	648		
Aspirin	1908/2062 (92.5%)	589/648 (90.9%)	0.86 (0.63–1.17)	0.34
Second antiplatelet	1829/2062 (88.7%)	545/648 (84.1%)	0.82 (0.64–2.05)	0.11
β-Blocker	1820/2062 (88.3%)	550/648 (84.9%)	0.78 (0.63–0.98)	0.036
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1685/2062 (81.7%)	501/648 (77.3%)	0.85 (0.66–1.09)	0.20
Statin	2001/2062 (97.0%)	607/648 (93.7%)	0.51 (0.34–0.77)	0.001
Cardiac rehabilitation referral	1735/2062 (84.1%)	497/648 (76.7%)	0.75 (0.61–0.91)	0.005

CI = confidence interval. * Women *v* men; adjusted for GRACE risk score quartile. ◆

have increased since 2010. Nevertheless, sex differences persist. More detailed qualitative evaluation of the reasons for these differences is needed to understand whether variances in management are justified, or whether strategies are needed to redress the imbalances.

Limitations

The strength of our study is that we examined data from 41 diverse centres across Australia, collected detailed information on the baseline characteristics of patients, and analysed prospectively collected data on clinical outcomes. There were nevertheless some limitations. First, senior hospital staff at participating hospitals were provided with real time electronic reports of key performance indicators of the effectiveness of their systems of care, and they could use this feedback to correct management deficits, meaning that these centres would not be representative of non-participating centres. However, in this case we will probably have underestimated differences in management and outcomes for men and women with STEMI. Second, follow-up to 6 months was not complete (80%), which may limit our ability to draw conclusions about outcomes at this point. This level of participation is, however, typical for an ongoing clinical quality registry study, and is comparable with those of large international ACS registries.[25] Further, there were no significant differences in the baseline characteristics of patients who were or were not followed up (online Appendix, table 7).

Conclusion

We found that both risk levels and outcomes for patients with STEMI in Australia are different for men and women. The mean GRACE risk score at admission was higher for women, and at every level of GRACE risk, women were less likely than men to receive invasive management and revascularisation. Women were also less likely to be prescribed preventive medicines after discharge, and had higher rates of major adverse cardiac events at 6 months. These differences do not seem medically justified. Future research should identify why they persist, the influences on decision making by health providers and health services that cause these differences, and strategies for redressing the disparities in treatment.

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