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Delayed Reperfusion and Poor Long-Term Outcomes for Women in an Australian STEMI Cohort

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Abstract

Background: Cardiovascular disease is an important cause of mortality and morbidity in Australian woman. Gender based differences exist in the treatment and outcomes of ischaemic heart disease.

Methods: We conducted an observational cohort study using prospectively collected data to examine whether sex-based differences exist in the presentation, treatment, and outcomes of patients with ST-elevation myocardial infarction (STEMI). The study involved 3,665 patients who presented to 12 hospitals between 2004–2018. Outcomes included time to reperfusion, major adverse cardiac events and all-cause mortality with follow up to 24 months.

Results: Women (n= 755, 20.6%) were older (65 vs 59yr, p<0.001) and more likely to have hypertension (60.4 vs 51.5%, p<0.001) and diabetes (33.6 vs 28.6%, p=0.021). Women had longer reperfusion times (symptom to reperfusion time 235 vs 215mins, p=0.002), which were driven by pre-hospital delays (symptom to door time 107 vs 95mins, p=0.001). In-hospital treatment times were not significantly different (door to table time women 79mins, men 75mins, p=0.074). Women had lower rates of multi-vessel disease (49 vs 53.2%, p<0.001) but were less likely to undergo stenting (86.7 vs 92.7%, p<0.001). Post discharge, women had lower rates of referral to cardiac rehabilitation (73.3 vs 82.7%, p=0.002) and experienced higher rates of complications (24mth MACE: 28 vs 17%, death: 27 vs 15%; p<0.001).

Conclusion: Women presenting with STEMI have prolonged reperfusion times and lower rates of cardiac stenting. Following discharge, women experience nearly twice the rates of MACE and death post STEMI. Factors contributing to these disparities require urgent attention.

Keywords: ST Elevation Myocardial Infarction, Epidemiology, Female, Sex Factors

Introduction

Cardiovascular disease is a leading cause of mortality and morbidity worldwide. In recent years significant advances have been made in the detection and treatment of coronary artery disease. With falling rates of coronary artery disease amongst men, a relative paucity of improvements amongst women has shifted research interest towards sex-based differences in cardiovascular disease.

Sex-based differences are known to exist in the clinical presentation and pathophysiology of ischaemic heart disease which may impact on treatment and outcomes [1-4]. Previous studies have demonstrated that women are more likely to present with atypical symptoms, at a later time, and at an older age than their male counterparts [2,5-8]. Recent registry studies have found that women with acute coronary syndromes are less likely to receive evidence-based treatment including revascularisation therapies [3,8-10]. Whilst there is agreement amongst observational studies that women have significantly higher mortality following myocardial infarction [6,11-13], there is no consensus as to if these differences can be explained by patient and presentation characteristics, or type of infarction, rather than gender.

To address this uncertainty, we examined the baseline characteristics, treatment and outcomes of patients presenting with ST-elevation myocardial infarction (STEMI) in an Australian registry cohort. We postulated that female patients would have a delayed presentation for medical care, but that intervention rates and outcomes following STEMI would be comparable between male and female patients.

Methods

We analysed data from a clinician-initiated registry established to monitor the provision of care and outcomes of patients presenting to our hospital network (Western Sydney Local Health District) with ST-elevation myocardial infarction. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

The cohort for the current analysis consisted of 3,665 consecutive patients who were prospectively enrolled between 2004–2018. The study was conducted within a government-defined health district and included one tertiary referral centre (Westmead Hospital, Sydney Australia) and eleven metropolitan hospitals from the surrounding region. The tertiary centre was the only hospital providing cardiac catheterisation STEMI facilities to the catchment area and pathways for the transfer of patients requiring reperfusion were well established. The protocols for these pathways have previously been published[14] and will not be restated in detail in this manuscript.

All patients who presented to hospitals in the catchment area within 12hrs of onset of chest pain with a provisional diagnosis of STEMI were transferred emergently to the catheterisation laboratory at the tertiary centre for primary percutaneous coronary intervention (PCI). Conventional electrocardiographic criteria were used for the diagnosis of STEMI, defined as either >0.1 mV of ST-elevation in two contiguous limb leads, 0.2 mV in two contiguous chest leads or presumed new left bundle branch block. No age or clinical limitations were applied to patient enrolment. Only patients with angiographically confirmed STEMI were enrolled in the registry.

Prior to cardiac catherisation all patients were given aspirin 300 mg orally. Patients undergoing PCI received a bolus of heparin 100 IU/kg intra-arterially during the procedure as well as a loading dose of a second antiplatelet agent immediately post angiography as per guidelines at the time. The use of a glycoprotein 2a/3b inhibitor prior to stent deployment was at the interventionalist's discretion, but encouraged if not otherwise contraindicated. Following intervention patients were monitored in the acute coronary care unit before transfer to the general cardiology ward. As per protocol at the tertiary centre, all patients underwent assessment of their left ventricular ejection fraction prior to discharge. To avoid underestimation of LVEF secondary to myometrial stunning LVEF was assessed at two days post-infarction.

Data Collection

Data were collected by trained research staff using standardised enrolment forms. Patient characteristics including demographics, comorbidities, electrocardiographic and biochemical data were collected from the medical record. Treatment details and postprocedural complications were also retrieved from the medical record. In patients who survived their index admission, rates of discharge medications and referral to cardiac rehabilitation were also examined, as was pre-discharge left-ventricular ejection fraction (LVEF).

Patients were contacted via phone at 30 days, 6, 12 and 24 months post discharge and interviewed using a standardised outcome questionnaire regarding hospital readmission, unscheduled revascularization procedures (PCI, CABG) and other significant morbidity or mortality. In addition, patient medical records were reviewed and collateral information sourced from general practitioners. Follow up data was not complete (96% at 30 days, 66% at 6mth, 60% at 12mth, 51% at 24mth). These rates are typical for an ongoing clinical registry with all-comers enrolment. Loss to follow up rates and timing did not differ significantly between genders. Median follow up time was 16.2 months (95% CI 14.3 – 18.1) as determined via the reverse Kaplan-Meier method.

Variables

Variables in the study were stipulated by the initial registry protocol. Clinical comorbidities of interest included hypertension (defined as blood pressure > 140/90 mmHg or on medical therapy for known hypertension), dyslipidaemia (total cholesterol > 5.5 mmol/L or on treatment for elevated cholesterol), diabetes mellitus, renal impairment (creatinine > 120 μmol/L), ischaemic heart disease (previous history of acute coronary syndrome, reversible ischaemia on stress testing or coronary artery disease on angiography), family history (first degree relative with myocardial infarction < 60 yrs), smoking status (current/previous/non-smoker), previous cerebrovascular accident or transient ischaemic attack (CVA/TIA) and previous cardiovascular intervention (CABG/PCI). Data were also collected on patient use of common cardiovascular medications on admission.

Patient presentation was assessed using a variety of different measures. Initial hospital of presentation and transportation mode were recorded to allow for adjustment of differences in treatment time. Baseline clinical features including blood pressure, heart rate, presence of pulmonary oedema, troponin (μg/L), electrocardiographic features (cardiac rhythm, presence of ST- elevation or LBBB, Q waves and infarct location) and findings on diagnostic angiography were recorded.

Treatment variables of interest included number of stents, total stent length and type of stent. Following PCI the need for additional interventions was recorded including placement of temporary pacing wires, intra-aortic balloon pumps, implanted cardiac defibrillators and CABG. Post-procedure medical therapy received by patients and uptake patterns of outpatient cardiac rehabilitation programs were also recorded.

Outcomes

Our primary outcome of interest was time to reperfusion which was assessed using two measures symptom-to-door time (S2DT) and door-to-table time (D2TT). We chose these measures as delay in treatment is frequently cited as a cause of sex-based differences. S2DT was defined as time in minutes from initial onset of symptoms consistent with myocardial infarction until presentation to hospital. D2BT was defined as time in minutes from initial presentation to hospital to first inflation of catheter balloon during PPCI.

Secondary outcomes of interest included rates of percutaneous coronary intervention; major adverse cardiac events (MACE, a composite of repeat myocardial infarction, stroke, all-cause death and need for emergency CABG); and all-cause mortality. The follow-up time points were as predefined by the registry (30 days, 6mths, 12mths, 24mths).

Statistical Analysis and Model

Categorical variables were compared with Pearson χ^2 or Fisher's exact tests as appropriate and reported as number and percentage. Continuous variables were compared using Student t-tests and are presented as mean and standard deviation. Nonparametric continuous variables were analysed with either Mann–Whitney U-test or Kruskal-Wallis test and reported using medians and interquartile ranges. Survival curves for MACE and all-cause mortality were plotted using Kaplan-Meier estimates and compared between genders using log-rank tests.

A number of clinical characteristics varied significantly by gender, highlighting the importance of adjusting for these factors. Cox proportional hazard models were used to examine the effect of multiple risk factors on MACE and mortality. Variables with a P value < 0.05 on univariate analysis that had been demonstrated in the literature to be associated with our primary or secondary outcomes were included in multivariate model. These included gender, age, hypertension, diabetes, smoking status, multivessel disease and renal impairment or cardiogenic shock on presentation. Prior to modelling, proportionality assumptions were verified using Schoenfeld residuals and examination of log plots. Collinearity was assessed using Spearman rank coefficients and examination of scatter plots with no significant correlations found between variables.

Rates of missing data were less that 5% for all variables in the model, where missing data were identified, patients were omitted from analyses. All statistical tests were 2-tailed with the significance level set at 0.05, confidence intervals (CI) were calculated at the 95% level. All statistical analyses were performed using SPSS 24.0 (IBM, Armonk, NY, USA).

Ethics

All participating sites were required to comply with local and national regulatory and privacy legislation. Informed consent was gained from patients prior to enrolment. Formal ethics approval was obtained from Western Sydney Local Health District Human Research Ethics Committee prior to commencement, and the authors attest that this is an accurate and full account of our study. This study conformed to the principles outlined in the Declaration of Helsinki 2013. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations[15] were followed in reporting our findings.

Results

Patient enrolment and flow throughout follow up is summarised in a CONSORT diagram in Figure 1. Differences in baseline clinical characteristics between genders are outlined in Table 1. Women presenting with STEMI (n=755, 20.6%) were older (women mean 65 years, standard deviation [SD] 13.6 years; men mean 59 years, SD 12.3 years; p<0.001) and more likely to have hypertension (women 60.4%, men 51.5%, p<0.001) and diabetes (women 33.6%, men 28.6%, p=0.021); but less likely to be a current or ex-smoker (women 51.8%, men 66.3%, p<0.001). Rates of previous ischaemic heart disease and coronary artery bypass grafting were similar between genders. Premorbid use of common preventative medications including ACE inhibitors, antiplatelet agents, beta blockers and statins was also similar. Women were more likely to be prescribed calcium channel blockers (women 11.8%, men 9%, p =0.026), nitrates (women 6.5%, men 4.3%, p=0.014) and diuretics (women 5.5%, men 2.7%, p<0.001).

Table 1: Baseline Characteristics of STEMI Patients by Gender

		Male	Female	P value
Clinical Characteristics				
Age		59	65	<0.001
Systolic BP		130	129	0.51
Diastolic BP		78	73	<0.001
Heart rate		78	80	0.045
Hypertension		1466 (51.5)	440 (60.4)	<0.001
Hypercholesterolaemia		1532 (53.9)	379 (52.2)	0.431
Diabetes	No	2022 (71.3)	481 (66.3)	0.021
	Type 1	66 (2.3)	24 (3.3)	
	Type 2	746 (26.3)	220 (30.3)	
Smoker	No	953 (33.7)	349 (48.2)	<0.001
	Previous	719 (25.4)	144 (19.9)	
	Current	1156 (40.9)	231 (31.9)	
Family history of early cardiac disease		1142 (40.9)	283 (39.9)	0.855
Previous ischaemic heart disease		672 (23.7)	175 (24.2)	0.794
Previous coronary artery bypass graft		105 (3.7)	18 (2.5)	0.136
Previous PCI		371 (13.1)	63 (8.7)	0.001
Previous CVA/TIA		120 (4.2)	51 (7.1)	0.002
Renal impairment		354 (12.2)	88 (11.7)	0.756
Lung disease		251 (10.2)	104 (16.9)	<0.001
Medications at Presentation				
Aspirin or dipyridamole		553 (19.5)	160 (22.2)	0.119
Antiplatelets		180 (6.4)	37 (5.1)	0.259
ACE inhibitors		364 (12.9)	81 (11.4)	0.303
Angiotensin receptor antagonists		326 (11.5)	121 (16.8)	<0.001
Beta blockers		363 (12.8)	111 (15.4)	0.080
Calcium channel blockers		254 (9.0)	85 (11.8)	0.026
Statin/lipid lowering agents		689 (24.3)	190 (26.3)	0.289

Diuretics		76 (2.7)	40 (5.5)	<0.001
Nitrates		120 (4.3)	47 (6.5)	0.014
Presentation Characteristics				
Presenting Hospital	Tertiary Centre	923 (31.7)	263 (34.8)	0.112
	Other	1987 (68.3)	492 (65.2)	
Transport	ETAMI/PAPA	853 (30.0)	220 (30.0)	0.015
	Ambulance	1161 (40.8)	336 (45.8)	
	Private Vehicle	829 (29.2)	178 (24.2)	
In-hours presentation		1838 (63.4)	485 (64.7)	0.549
Rhythm	Sinus	2484 (85.9)	613 (81.8)	0.001
	Atrial fibrillation	108 (3.7)	26 (3.5)	
	VT/VF	102 (3.5)	27 (3.6)	
	Bradycardia	150 (5.2)	55 (7.3)	
	LBBB	14 (0.5)	6 (0.8)	
	1st deg AVB	14 (0.5)	4 (0.5)	
	2nd deg AVB	4 (0.1)	2 (0.3)	
	3rd deg AVB	17 (0.6)	16 (2.1)	
Infarct region on ECG	Anterior	1051 (36.3)	288 (38.1)	0.147
	Inferior	1272 (43.9)	324 (42.9)	
	Lateral	87 (3.0)	26 (3.4)	
	Anterior + lateral	258 (8.9)	50 (6.6)	
	LBBB	10 (0.3)	7 (0.9)	
	Inferior + lateral	173 (6.0)	49 (6.5)	
	Inferior + anterior	47 (1.6)	11 (1.5)	
Angiography	Normal/Minor	8 (0.3)	11 (1.5)	<0.001
	1VD	1347 (46.5)	371 (49.5)	
	2VD	824 (28.5)	202 (27.0)	
	3VD/LMD	717 (24.8)	165 (22.0)	
Cardiogenic shock		317 (21.9)	113 (28.6)	0.006

Abbreviations: ACE inhibitor: Angiotensin Converting Enzyme Inhibitor, AVB: atrioventricular block, CVA/TIA: Cerebrovascular Accident/Transient Ischaemic Attack; ETAMI: Emergency Triage of Acute Myocardial Infarction, PAPA: Pre-hospital Assessment for Primary Angioplasty, PCI: Percutaneous Coronary Intervention; STEMI: ST-Elevation Myocardial Infarction, 1VD: single vessel disease, 2VD: double vessel disease, 3VD/LMD: triple vessel or left main disease.

At time of initial presentation to hospital, women with STEMI were more likely to be in acute pulmonary oedema (women 16.6%, men 11.5%, p<0.001), they also had higher rates of dysrhythmias (bradycardia: women 7.3%, men 5.2%; complete heart block: women 2.1%, men 0.6%; overall p<0.001). Baseline electrocardiographic findings prior to catheterisation did not differ significantly between groups with similar distributions of infarct region (p=0.147) and type of morphological changes (ST elevation, LBBB; p=0.102). Biochemical markers of cardiac damage differed significantly between sexes with higher pre-PCI troponin values in women (women 3.26μg/L, men 2.12μg/L, p=0.006), post procedural troponin values were also higher (women 24.6μg/L, men 19.49μg/L) although this did not meet statistical significance (p=0.158). Women were more likely to present in cardiogenic shock (women 28.6%, men 21.9%, p=0.006) and require temporary pacing wires (women 8%, men 3.3%, p<0.001) and circulatory supports such as intra-aortic balloon pumps (women 10.8%, men 7%, p=0.001).

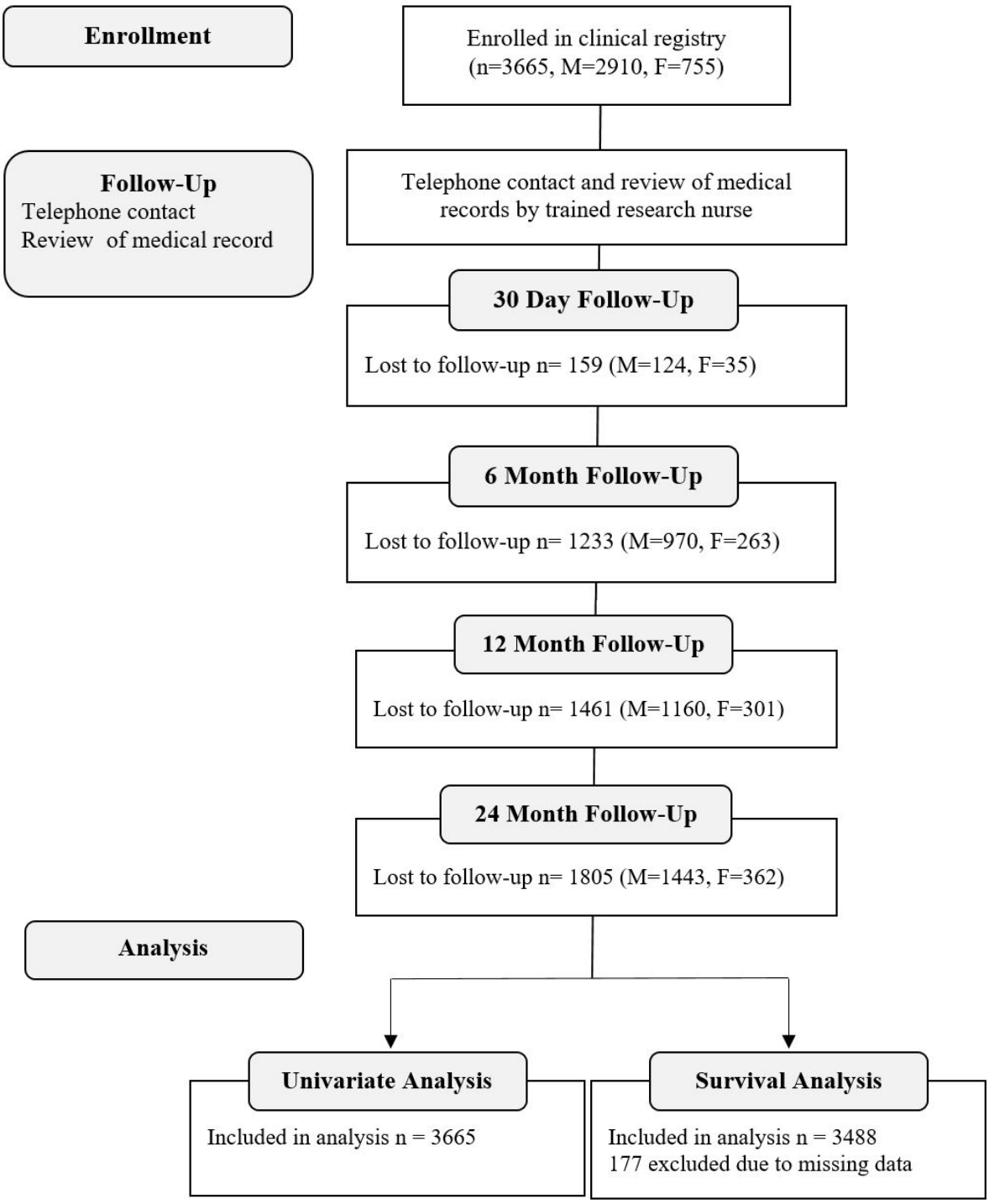


Figure 1: CONSORT Flow Diagram

Women had longer overall reperfusion times (symptom to reperfusion time [S2RT] median women 235mins, men 215mins, p=0.002), which was driven by pre-hospital delays (symptom to door time [S2DT] median: women 107mins, men 95mins, p=0.001). In-hospital treatment times did not differ substantially (door to table time [D2TT] median women 79mins, men 75mins, p=0.074). Women had lower rates of multi-vessel or left-main disease (women 49%, men 53.2%, p<0.001) but were less likely to undergo PCI (86.7% vs 92.7%, p<0.001). When women did undergo stenting, their procedure was less likely to be successful in restoring TIMI3 flow (women 87.7%, men 91.3%, p=0.01). There was no significant difference in length of stay (women median 5 days, men median 5 days, p=0.981), left ventricular impairment (LVEF ≤40%: women 20.8%, men 23.9%, p=0.134) or cause of death (p=0.671).

In patients who survived their index admission, women had lower rates of referral to cardiac rehabilitation (women 73.3%, men 82.7%, p=0.002) and were less likely to receive an automatic implantable cardiac defibrillator prior to discharge

(women 3.0%, men 5.4%, p<0.001). As shown in Figure 2, women experienced consistently higher rates of MACE and mortality throughout the study period (24mth MACE: women 28%, men 17%, p<0.001; 24mth mortality: women 27%, men 15%, p<0.001). The Kaplan–Meier curves in Figure 3 graphically depict differences in time to a) MACE and b) death between males and females in the study cohort (log rank p <0.001 for both). In unadjusted analyses, women were at higher risk of both MACE (HR 1.46, p<0.001, confidence interval [CI] 1.22–1.75) and death (HR 1.91, p<0.001, CI 1.53–2.38). After adjustment for differences in baseline comorbidities, female gender was not independently associated with higher rates of MACE or all-cause mortality at 24 months post STEMI. Diabetes, multivessel disease, renal impairment and cardiogenic shock were all associated with higher likelihood of MACE and death (Table 2).

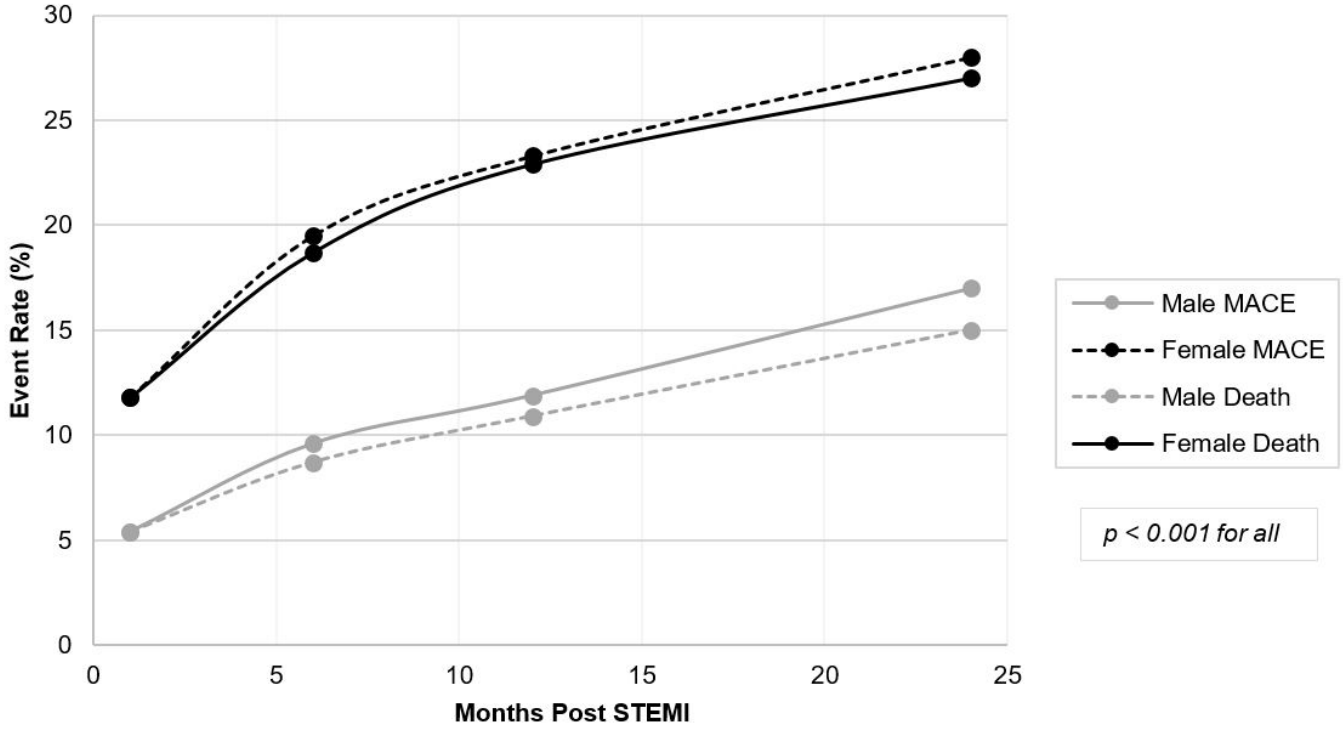
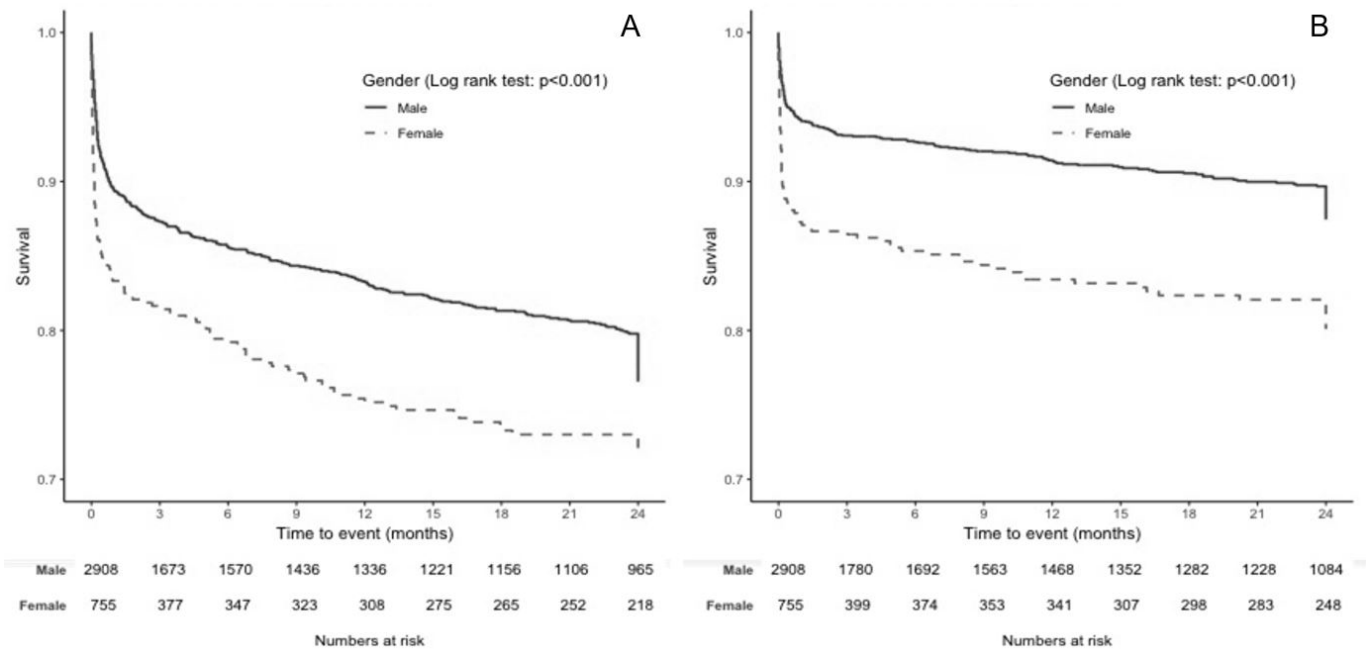


Figure 2: Rates of Major Adverse Coronary Events & Mortality Post STEMI by Gender

	30 day		**6mth**		**12mth**		**24mth**	
	Male	Female	Male	Female	Male	Female	Male	Female
MACE (n,%)	150 (5.4)	85 (11.8)	186 (9.6)	96 (19.5)	208 (11.9)	106 (23.3)	249 (17.0)	110 (28.0)
Death	150 (5.4)	85 (11.8)	169 (8.7)	92 (18.7)	191 (10.9)	104 (22.9)	220 (15.0)	106 (27.0)
Stroke	14 (0.5)	7 (1.0)	3 (0.2)	0 (0.0)	3 (0.2)	1 (0.2)	7 (0.5)	0 (0.0)
Repeat infarct	19 (0.7)	6 (0.8)	14 (0.7)	4 (0.8)	14 (0.8)	1 (0.2)	22 (1.5)	4 (1.0)
CABG	99 (3.6)	20 (2.8)	29 (1.5)	8 (1.6)	11 (0.6)	5 (1.1)	9 (0.6)	0 (0.0)
Mortality (n,%)	150 (5.4)	85 (11.8)	169 (8.7)	92 (18.7)	191 (10.9)	104 (22.9)	220 (15.0)	106 (27.0)



(A) Kaplan-Meier curve for Major Adverse Coronary Events Post STEMI by Gender

(B) Kaplan-Meier curve for All-Cause Mortality Post STEMI by Gender

Figure 3: Kaplan Meier Survival Estimates of Secondary Outcomes (MACE, Mortality)

Table 2: Cox Multivariate Hazard Models of MACE and Mortality at 24 Months PostSTEMI

	Model 1: MACE		Model 2: Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (Female)	1.15 (0.85 - 1.58)	0.37	1.04 (0.71 - 1.52)	0.85
Age (per 10yrs)	1.26 (10.2 - 10.4)	<0.001	1.50 (10.4 - 10.7)	<0.001
Hypertension (Yes)	0.89 (0.68 - 1.17)	0.41	0.76 (0.54 - 1.08)	0.13
Diabetes (Yes)	1.41 (1.07 - 1.85)	0.01	1.71 (1.22 - 2.41)	0.01
Smoking Status (Exsmoker)	0.61 (0.44 - 0.87)	0.01	0.56 (0.36 - 0.87)	0.01
Smoking Status (Current)	0.73 (0.53 - 0.99)	0.05	0.67 (0.44 - 1.01)	0.56
Renal Impairment (Yes)	1.66 (1.22 - 2.26)	0.001	2.03 (1.41 - 2.92)	<0.001
Angiography (Multivessel)	53.1 (0.01 - 341)	0.87	17.8 (0.01 - 104)	0.89
Cardiogenic shock (Yes)	2.97 (2.27 - 3.87)	<0.001	4.6 (3.27 - 6.59)	<0.001

Discussion

Our analysis of a large contemporary Australian registry describes several key differences between male and female patients presenting with STEMI. We found that at time of presentation, women were older and more likely to have comorbidities than their male counterparts. Women had significantly longer reperfusion times, a finding which was driven predominantly by pre-hospital delays. Women were less likely to undergo coronary angioplasty and were more likely to experience significant heart failure, cardiogenic shock and dysrhythmias in hospital. In those who survived their index admission, rates of major adverse cardiac events and mortality were two-fold higher in women, this increased risk persisted throughout our 24 month follow up period.

Rates of comorbidities amongst our study population were high, however, similar to local cohorts who have also recorded a higher average age and comorbidity burden amongst female patients [5-7,16]. This is concerning trend given emerging research highlighting the accelerated atherosclerotic effects of factors such as smoking, hypertension and diabetes in post-menopausal wo men [1,12,17].

Our finding of a longer overall reperfusion time and longer symptom to door time is in keeping with several international studies showing that women with STEMI present later for treatment [3,13,18]. We did not find sex-related difference in the in-hospital treatment times in our study, though note that these have been reported to be longer for women in other studies [3,9,10,19-22]. Traditionally differences in symptoms have been suggested to contribute to delays in both help seeking and diagnosis leading to delayed recognition of acute coronary syndromes in women [23-26]. Cultural beliefs that ischaemic heart disease predominantly affects men may also contribute to under-recognition [6, 27]. Public health messages need to be encouraged and amplified to improve awareness of ischemic heart disease in women.

We found lower rates of coronary intervention amongst women with STEMI (PCI: women 86.7%, men 92.7%, p<0.001) and when women did undergo intervention, their procedure was less likely to be successful in restoring adequate coronary flow (TIMI3 flow: women 87.7%, men 91.3%, p=0.01). Similar results have been observed both locally (Khan et. al. n = 2898; PCI: men 77.8 %, women 65%)[6] and internationally (Radovanovic et. al. PCI: 40.3% men, 30.9% women) [5]. Compared to these studies our rates of PCI are relatively high, this is likely a reflection of the metropolitan setting of our study, relative preference for primary PCI over other reperfusion therapies and registry inclusion criteria. Regardless, the reasons for lower rates of stenting amongst women are uncertain and it remains unclear if such a difference is clinically justifiable. Lower rates of stenting may be a reflection of delays in presentation which may render a procedure futile, unsuitable coronary anatomy, or if comorbidities are felt produce an unfavorable safety profile. Whether these characteristics are more common in women requires further investigation. Angiographically rates of non-obstructive coronary disease within our female cohort were higher than in men (women 1.5%, men 0.3%, p<0.001). This may partially explain the lower rates of intervention seen in our study and raises questions as to the underlying mechanism of ischaemia in these patients.

Whilst women are more likely than men to have angiographically normal coronary arteries at time of STEMI [2, 4] this lack of obstructive coronary disease does not equal an absence of atherosclerosis or a lower risk phenotype. Plaque burden may be underestimated if outer remodeling has occurred and alternative methods of imaging such as optical coherence tomography or intravascular ultrasound may provide valuable information to re-stratify risk. Alternate mechanisms of ischaemia such as vasospasm, plaque erosion or coronary microvascular dysfunction [1,4] are also thought to contribute to a greater degree in women and may mean that traditional angiography is inadequate for stratification of cardiac risk in women. These alternative mechanisms, particularly coronary microvascular dysfunction, are increasingly thought to be linked with poor prognosis and elevated rates of heart failure post infarction [28-30] and may explain the higher rates of acute pulmonary oedema and cardiogenic shock seen within our female cohort. Despite having less obstructive coronary disease women in our study were more likely to suffer major adverse cardiac events and death throughout the study period. By conflating non-obstructive coronary disease with non-significant disease, we neglect an important opportunity for disease prevention in women.

There is ongoing uncertainty regarding if the adverse outcomes seen amongst women with STEMI can be accounted for by patient factors [23,31-34]. Our findings are consistent with a recent Australian study by Khan et. al. which found persistently higher rates of MACE and mortality in female STEMI patients despite adjustment for presentation time and GRACE score [6]. These findings confirm and are consistent with the study by Khan et. al., though outcome differences by sex at 24 months were attenuated in our study by adjusting for covariates, namely increased age and comorbidity burden. Our study also provides additional information on sex differences in the pre-hospital period compared to an in-hospital setting. Concerningly, despite being at increased risk of mortality, women are receiving less evidence-based treatment and are less likely to be referred to secondary preventative programs such as cardiac rehabilitation. These differences in clinical care are not justifiable and the reasons behind them need to be better understood as they appear to be driven by differences in health provider implementation of guidelines.

The strengths of our current study are that we collected detailed information on consecutive patients, we enrolled from a range of both urban and regional hospitals, data was analysed prospectively and we completed an extended follow up period to maximise our yield of clinically relevant outcomes. Despite these strengths, our findings should be interpreted within the context of the limitations of our analysis. Given our observational study design, we are inherently unable to drawn definitive causal links. We can only speculate on the reasons for the longer reperfusion times seen in women, as registry data did not include presenting

symptoms or qualitative information on the decision making of treating clinicians, factors that have been suggested to contribute to observed sex-based differences in treatment times in STEMI [35-37]. Follow up data to 24 months was not complete which is reflective the prospective nature of the registry with ongoing data collection, as well as high rates of migration and itineracy in the study catchment area which complicate long term follow up. During our study period (2004-2018) several key changes in interventional practice have occurred including the introduction of potent P2Y12 inhibitors, transition to radial access and trends towards complete revascularization at time of infarct. This may partially explain differences between our study and more contemporary trials [3,38]. Lastly, the results of our study as specific to the STEMI population undergoing primary PCI and may not be generalizable to other forms of acute coronary syndrome or reperfusion modes such as thrombolysis.

Conclusion

Women presenting with STEMI are older, have prolonged reperfusion times and have lower rates of cardiac stenting despite anatomically simpler disease at time of presentation. Post discharge, women experience nearly twice the rates of major adverse coronary events and death post STEMI. These differences are concerning and require further investigation.

Our findings highlight the need for a multifaceted approach to addressing cardiovascular disease in women. Increased public education is needed to improve recognition of symptoms and timeliness of presentation to hospital by women with STEMI. Clinicians must remain attentive to the need for aggressive management of cardiovascular risk factors in females and consider their own decision-making processes when caring for women with STEMI.

Further research is required to identify factors contributing to late presentation and low angioplasty rates in women. A focus on gender-sensitive research and exploration of pathophysiological differences in coronary artery disease in women, including myocardial infarction in non-obstructive coronary disease and coronary microvascular dysfunction, will be important in addressing observed disparities.

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