

ORIGINAL RESEARCH

# Sex Differences in Prehospital Delays in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention

Julia Stehli <sup>id</sup>, MD; Diem Dinh, PhD; Misha Dagan <sup>id</sup>, MMed(Epi), MD; Stephen J. Duffy <sup>id</sup>, MBBS, PhD; Angela Brennan, RN; Karen Smith, PhD; Emily Andrew <sup>id</sup>, MBiostat; Ziad Nehme, PhD; Christopher M. Reid <sup>id</sup>, PhD; Jeffrey Lefkovits, MBBS; Dion Stub <sup>id</sup>, MBBS, PhD; Sarah Zaman <sup>id</sup>, MBBS, PhD

**BACKGROUND:** Women with ST-segment–elevation myocardial infarction experience delays in reperfusion compared with men with little data on each time component from symptom onset to reperfusion. This study analyzed sex discrepancies in patient delays, prehospital system delays, and hospital delays.

**METHODS AND RESULTS:** Consecutive patients with ST-segment–elevation myocardial infarction treated with percutaneous coronary intervention across 30 hospitals in the Victorian Cardiac Outcomes Registry (2013–2018) were analyzed. Data from the Ambulance Victoria Data warehouse were used to perform linkage to the Victorian Cardiac Outcomes Registry for all patients transported via emergency medical services (EMS). The primary end point was EMS call-to-door time (prehospital system delay). Secondary end points included symptom-to-EMS call time (patient delay), door-to-device time (hospital delay), 30-day mortality, major adverse cardiovascular events, and major bleeding. End points were analyzed according to sex and adjusted for age, comorbidities, cardiogenic shock, cardiac arrest, and symptom onset time. A total of 6330 (21% women) patients with ST-segment–elevation myocardial infarction were transported by EMS. Compared with men, women had longer adjusted geometric mean symptom-to-EMS call times (47.0 versus 44.0 minutes;  $P<0.001$ ), EMS call-to-door times (58.1 versus 55.7 minutes;  $P<0.001$ ), and door-to-device times (58.5 versus 54.9 minutes;  $P=0.006$ ). Compared with men, women had higher 30-day mortality (odds ratio [OR], 1.38; 95% CI, 1.06–1.79;  $P=0.02$ ) and major bleeding (OR, 1.54; 95% CI, 1.08–2.20;  $P=0.02$ ).

**CONCLUSIONS:** Female patients with ST-segment–elevation myocardial infarction experienced excess delays in patient delays, prehospital system delays, and hospital delays, even after adjustment for confounders. Prehospital system and hospital delays resulted in an adjusted excess delay of 10 minutes compared with men.

**Key Words:** first medical contact ■ ischemic time ■ prehospital delay ■ sex discrepancies ■ ST-segment–elevation myocardial infarction

**T**imely revascularization with percutaneous coronary intervention (PCI) is a critical component of improving outcomes in ST-segment–elevation myocardial infarction (STEMI).<sup>1–4</sup> During the past decades, major improvements in reperfusion times have been achieved.<sup>5,6</sup> However, healthcare services have

focused on improving door-to-device (DTD) times, with little impact on system delays that occur before a patient arrives at the hospital.<sup>7–9</sup> The latter can be substantial and is often difficult to assess because of multiple time components.<sup>10</sup> Of particular concern has been the finding that women with STEMI have

Correspondence to: Sarah Zaman, MBBS, PhD, Westmead Applied Research Centre, Hawkesbury Road, Westmead, Sydney, Australia 2145. E-mail: sarah.zaman@sydney.edu.au

For Sources of Funding and Disclosures, see page 10.

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## CLINICAL PERSPECTIVE

### What Is New?

- Female patients with ST-segment–elevation myocardial infarction (STEMI) transported to a hospital via emergency medical services have longer patient delays, prehospital healthcare delays, hospital delays, and total healthcare delays (the sum of prehospital healthcare and hospital delays) compared with male patients with STEMI.
- Two thirds of the total delay in women result from healthcare delays with female patients with STEMI experiencing an adjusted excess healthcare system delay of 10 minutes compared with men.
- This delay likely represents a complex construct of differences in presentation as well as patient and professional bias.

### What Are the Clinical Implications?

- Specific strategies are needed to address delays in STEMI care for female patients.
- Female patients' awareness of their risk of cardiovascular disease and heart attack symptoms should continue to be targeted with public health campaigns.
- Education of healthcare professionals on the potential role of sex bias should include all providers involved in STEMI care, from the provider receiving the emergency call to the ambulance officers and interventional cardiologist.

## Nonstandard Abbreviations and Acronyms

<b>DTD</b>	door-to-device
<b>FMC</b>	first medical contact
<b>VCOR</b>	Victorian Cardiac Outcomes Registry

significantly longer ischemic times with delays in reperfusion.<sup>11,12</sup> These delays have been related to both hospital and prehospital delays.<sup>13–16</sup> Prehospital delays consist of the time from STEMI symptom onset to arrival at the door of a PCI-capable hospital. They consist of a patient's delay from symptom onset until first medical contact (FMC) and a prehospital healthcare delay from FMC until arrival at a hospital. In particular, patient delays for women have been targeted by public awareness campaigns to increase women's early recognition of myocardial infarction symptoms and the need to activate emergency services.<sup>15,17</sup> In patients with STEMI who travel via emergency medical services (EMS), the prehospital healthcare times are made up of

multiple components, including EMS call to arrival time and ECG acquisition, scene time, and scene-to-door time.<sup>8</sup> Delays at each point can result in reperfusion delays and longer ischemic times. Sex differences in each component of the symptom-to-door time have not been well studied.

We therefore aimed to assess sex differences in prehospital delays in patients with STEMI transported by EMS and their impact on clinical outcomes. This is of critical importance as we need to identify the reasons for delays still observed in women with STEMI to design and implement strategies to overcome them.

## METHODS

### Data Availability Statement

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the VCOR (Victorian Cardiac Outcomes Registry) Data Access, Research and Publications Committee at [vcor@monash.edu](mailto:vcor@monash.edu).

### Study Design and Patient Population

From 2013 to 2018, consecutive patients treated with PCI for STEMI were prospectively enrolled into the VCOR. VCOR is an Australian, state-based clinical quality registry designed to monitor the performance and outcomes of PCI in Victoria. VCOR was established in 2012 and is engaged at 30 Victorian hospitals (13 public [ie, government funded] and 17 private) with all patients undergoing successful or attempted PCI entered into the registry.<sup>18</sup> VCOR collects baseline demographic, procedural characteristics, in-hospital, and 30-day outcomes on all patients who undergo PCI at a given facility through a secure web-based data collection system.<sup>19</sup> Data integrity is ensured with regular audit activities conducted by the central registry. VCOR is funded by the Victorian Department of Health and Human Services.

Data from the Ambulance Victoria Data warehouse were used to perform data set linkage to VCOR for all patients with STEMI. Ambulance Victoria is the state-wide EMS in Victoria, Australia, covering 227 000 km<sup>2</sup> with a population of >6.3 million residents. Paramedics in Victoria complete an electronic patient care record at the conclusion of each case, including timestamps from receipt of the phone call to the Triple Zero (000) emergency number until off stretcher at the hospital. Data from these records and the computer-aided dispatch system are uploaded into a data warehouse.<sup>20</sup> Most Ambulance Victoria paramedics are trained to the advanced life support level. Mobile intensive care ambulance paramedics have a higher clinical skill set and provide advanced management of cardiac

conditions. Until 2016, only mobile intensive care ambulance EMS were equipped with monitors capable of 12-lead ECGs, and all other advanced life support paramedics carried monitors capable of 3-lead ECGs. In 2016, all paramedics in Victoria were equipped with monitors capable of 12-lead ECGs and wireless transmission technology.

To obtain patient socioeconomic status, residential postcodes recorded in VCOR were linked with the Index of Relative Socioeconomic Disadvantage developed by the Australian Bureau of Statistics from data collected in the national census in 2016. Each postcode is allocated an Index of Relative Socioeconomic Disadvantage score based on a weighted combination of factors including household income, unemployment rate, and home and vehicle ownership, with a low score indicating high socioeconomic disadvantage. All postcodes in the state of Victoria are ranked according to Index of Relative Socioeconomic Disadvantage score and classified by deciles.<sup>21,22</sup>

The study was approved by the Institutional Human Research Ethics Committee with an opt-out consent.

### Inclusion and Exclusion Criteria

Consecutive patients who were transported to a hospital by Ambulance Victoria and received successful or attempted PCI for a STEMI were included. At the time of entering the patient into the VCOR database, STEMI was defined as elevated biomarkers and new or presumed new ST-segment elevation in  $\geq 2$  contiguous leads. The clinical definition was based on the Fourth Universal Definition of Myocardial Infarction.<sup>23</sup> Preprocedural creatinine was collected up to 60 days before the PCI, and the Cockcroft-Gault formula was used to determine estimated glomerular filtration rate. Left ventricular ejection fraction (LVEF) was collected during the index admission. Normal LVEF was defined as LVEF  $> 50\%$ , moderate dysfunction as LVEF 35% to 44%, and severe dysfunction as LVEF  $< 35\%$ . New heart failure was defined as LVEF  $< 45\%$  with clinical evidence of heart failure. Complex lesions included type B2 and C lesions according to the American College of Cardiology/American Heart Association classification guidelines.

Only patients in whom VCOR and Ambulance Victoria data linkage was performed were included. Patients were excluded if they had (1) missing time data, (2) symptom onset while already admitted to hospital, (3) presented after 12 hours from symptom onset, (4) underwent thrombolysis before PCI, or (5) were transported by Ambulance Victoria after the PCI (and not before). Specifically, for the analysis of DTD time, patients were excluded if they were transferred to a non-PCI-capable hospital and thereafter underwent interhospital transfer (Figure 1).

### Definition of Time Intervals

Figure 2 gives an overview of the ischemic time spans and delays assessed.

#### Time Spans

Symptom-to-EMS call time was defined as time from STEMI symptom onset recorded in the medical records to the time when Ambulance Victoria received the first call, which was recorded in the computer-aided dispatch system. Ambulance arrival at scene was used as FMC. EMS call-to-FMC time was defined as the time interval between Ambulance Victoria receiving the first phone call until arrival of the first team at the scene. FMC-to-ECG time was defined as time interval from arrival of the first team at the scene to acquisition of a 12-lead ECG. The time of ECG acquisition was used as time of STEMI diagnosis. ECG-to-departure time was defined as time from acquisition of a 12-lead ECG to departure from the scene. Scene time was defined as the entire time spent with the patient at their pick-up location, from FMC to departure time of the transporting team. Departure-to-door time was defined as time from departure from the scene to arrival at the PCI-capable hospital. DTD time was defined as time from arrival at the PCI-capable hospital to time of reperfusion of the culprit coronary artery. Total ischemic time was defined as time from symptom onset to reperfusion of the culprit artery.

#### Time Delays

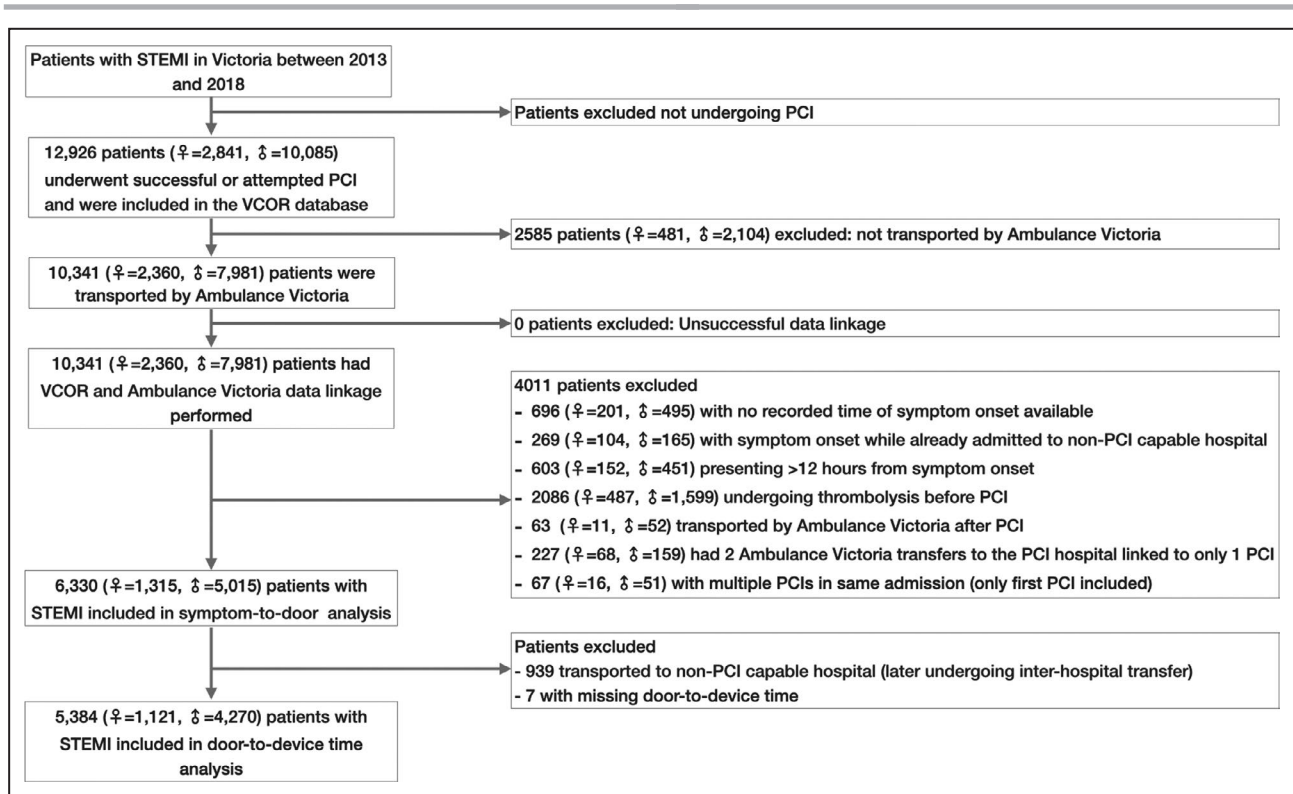
Patient delay was defined as symptom-to-EMS call time. Prehospital system delays were defined as the timespan between the phone call to Ambulance Victoria until arrival at the PCI-capable hospital (EMS call-to-door time). Hospital delay was defined as DTD time. Healthcare delay was the sum of prehospital system delay and hospital delay.

#### Guideline-Recommended Times

The FMC-to-device time was defined as time from EMS arrival at the scene until reperfusion of the culprit artery.<sup>4</sup> The FMC-to-ECG time was defined as time from EMS arrival at the scene until acquisition of an ECG.<sup>2</sup>

### Primary and Secondary Outcomes

The primary end point was EMS call-to-door time (pre-hospital EMS-related system delay). Secondary end points included each component of the prehospital system delay as well as the patient, hospital system, and healthcare delays (Figure 2). Secondary outcomes included 30-day all-cause mortality, major adverse cardiovascular events (consisting of all-cause death,



**Figure 1. Inclusion and exclusion criteria.**

Overview of the patients included. A total of 6330 patients (21% women) were included in the final analysis for baseline criteria, outcomes, and symptom-to-door time; 5384 patients were included for door-to-device time analysis. PCI indicates percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and VCOR, Victorian Cardiac Outcome Registry.

new or recurrent myocardial infarction, stent thrombosis, or target vessel revascularization), major adverse cardiovascular and cerebrovascular events (consisting of major adverse cardiovascular events and stroke), major bleeding (consisting of types 3 and 5 according to the Bleeding Academic Research Consortium definition),<sup>24</sup> recurrent myocardial infarction, new heart failure (defined according to clinical signs), and new renal impairment.

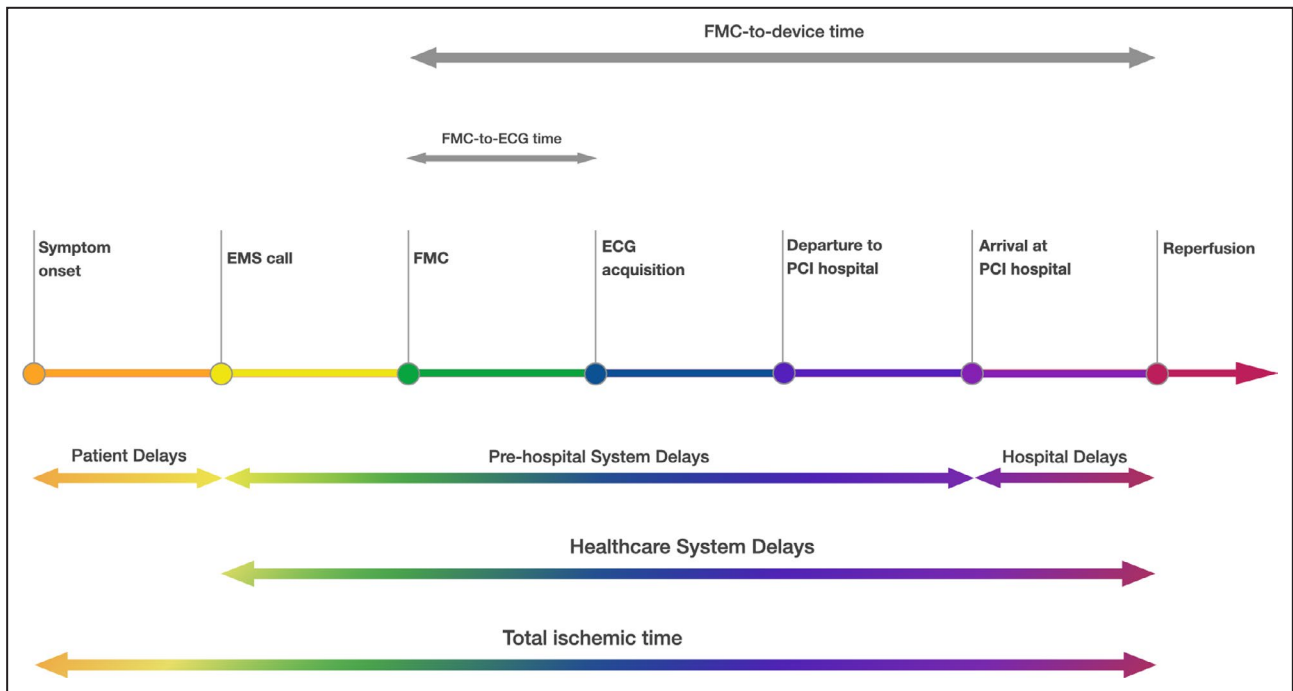
According to the American College of Cardiology/American Heart Association guidelines, the percentage of patients who were transported to a PCI-capable facility achieving an FMC-to-device time of  $\leq 90$  minutes was calculated and compared between sexes.<sup>4</sup> According to the European Society of Cardiology guidelines, the percentage of patients achieving an FMC-to-ECG time of  $\leq 10$  minutes was compared between sexes.<sup>2</sup>

## Statistical Analysis

VCOR and Ambulance Victoria data linkage was performed with prehospital care records captured electronically by Ambulance Victoria using identifier variables (names, date of birth, date of hospital arrival). Match scores  $>0.75$  were assumed to

be true. Associations in categorical variables were analyzed with chi-square or Fisher exact tests as appropriate and expressed as number and percentage. Continuous variables were analyzed with *t* tests and expressed as mean and standard deviation. Univariable and multivariable associations with sex were determined by logistic regression. Because the distributions of times were highly skewed, their data were log-transformed for analysis and then back-transformed to determine an estimated geometric mean. The geometric mean was adjusted for age, diabetes mellitus, estimated glomerular filtration rate, previous PCI and/or coronary artery bypass grafting, history of peripheral vascular disease and cerebrovascular disease, LVEF, cardiogenic shock, out-of-hospital cardiac arrest requiring intubation, and time of symptom onset (night versus day). The same variables were determined a priori to be included in the multivariable models. The variables forced into and retained in the models were determined based on prior literature and experience that these factors are known to influence major adverse cardiovascular events and all-cause mortality. Statistical analyses were performed using Stata version 16 with  $P < 0.05$  considered statistically significant.





**Figure 2. Overview of time intervals from symptom onset to reperfusion.**

Overview of the ischemic time spans and delays assessed. The primary end point was EMS call-to-door time (prehospital EMS-related system delay). Secondary end points included each component of the prehospital system delay as well as the patient, hospital, and healthcare delays. EMS indicates emergency medical services; FMC, first medical contact; and PCI, percutaneous coronary intervention.

## RESULTS

### Baseline, Procedural, and Discharge Data

A total of 12 926 patients with STEMI underwent successful or attempted PCI and were included in the VCOR database. Of these, 10 341 patients (23% female) were transported by Ambulance Victoria and were successfully linked with Ambulance Victoria data. Figure 1 gives an overview of the patients: 6330 patients (21% female) were included in the final analysis for baseline criteria, outcomes, and symptom-to-door time; 5384 patients were included for DTD time analysis. Table 1 shows baseline, procedural, and discharge characteristics. Female patients were significantly older and had more comorbidities than male patients. There was no sex difference in socioeconomic status. Radial access was used significantly less often in female than male patients. Female patients received significantly lower rates of secondary prevention medications compared with male patients.

### EMS Data

Ambulance Victoria use rates were 83% in female patients and 79% in male patients in the entire VCOR cohort (before database matching; odds ratio [OR], 1.29; 95% CI, 1.16–1.44;  $P < 0.001$ ; not shown in tables). Ambulance Victoria data including prehospital ECG notification, proportion with transport to a

non-PCI-capable hospital, and unit skill set are displayed in Table 2. Prehospital ECG notification was performed in 61.9% of female patients compared with 65.1% of male patients ( $P = 0.032$ ).

### Time Analyses

Patient, prehospital, and hospital delays are displayed in Table 3 and Figure 3.

#### **Patient Delay (Symptom-to-EMS Call Time)**

Both unadjusted and adjusted geometric mean symptom-to-EMS call times were significantly longer in women compared with men (adjusted, 47.0 versus 44.0 minutes;  $P < 0.001$ ).

#### **Primary End Point: Prehospital System Delay (EMS Call-to-Door Time)**

Both unadjusted and adjusted geometric mean EMS call-to-door times were significantly longer in women than men (adjusted, 58.1 versus 55.7 minutes;  $P < 0.001$ ). Adjusted geometric mean for EMS call-to-FMC, ECG-to-departure, and total scene time were significantly longer in women than men. There were no sex differences in the adjusted geometric mean for FMC-to-ECG time and departure-to-door time.

**Table 1. Baseline and Discharge Characteristics According to Sex**

	Total Patients With STEMI, n=6330	Female Patients, n=1315	Male Patients, n=5015	P Value
Age, y	62.9±12.8	68.4±13.3	61.5±12.3	<0.001
Low socioeconomic status	1207 (19.4)	273 (21.0)	934 (19.0)	0.09
BMI, kg/m <sup>2</sup>	27.5 (24.7–30.8)	27.1 (23.5–31.1)	27.7 (24.9–30.6)	<0.001
Diabetes mellitus	1002 (15.8)	236 (17.9)	766 (15.3)	0.02
eGFR ≤45 mL/min	493 (7.8)	239 (18.2)	254 (5.1)	<0.001
Moderate–severe LVEF impairment	1720 (29.1)	332 (27.3)	1388 (29.5)	0.13
Previous CABG and/or PCI	820 (13.0)	123 (9.4)	697 (13.9)	<0.001
Cerebrovascular disease	223 (3.5)	65 (4.9)	158 (3.2)	0.002
Peripheral vascular disease	139 (2.2)	34 (2.6)	105 (2.1)	0.28
Oral anticoagulant therapy	173 (2.7)	49 (3.7)	124 (2.5)	0.01
Onset of symptoms 7 AM to 8 PM	4128 (65.2)	836 (63.6)	3292 (65.6)	0.16
Cardiogenic shock or cardiac arrest requiring intubation	758 (12.0)	150 (11.4)	608 (12.1)	0.48
Radial access	3506 (55.4)	640 (48.7)	2866 (57.1)	<0.001
PCI success	5958 (94.1)	1229 (93.5)	4729 (94.3)	0.25
Glycoprotein IIb/IIIa inhibitor	2374 (37.5)	425 (32.3)	1949 (38.9)	<0.001
Mechanical ventricular support	191 (3.0)	19 (1.4)	172 (3.4)	<0.001
Referral to cardiac rehabilitation	4987 (78.8)	995 (75.7)	3992 (79.6)	0.002
Discharge medication				
Aspirin	5784 (98.1)	1171 (97.8)	4613 (98.2)	0.41
Thienopyridine	1554 (26.4)	355 (29.7)	1199 (25.5)	0.004
Ticagrelor	4219 (71.6)	811 (67.9)	3408 (72.6)	0.001
β-blockers	5132 (87.2)	1014 (84.9)	4118 (87.8)	0.008
ACEI/ARB	4956 (84.2)	977 (81.8)	3979 (84.9)	0.010
Statin	5702 (96.8)	1128 (94.4)	4574 (97.4)	<0.001

Data are presented as number (percentage), mean±SD, or median (interquartile range). LVEF data were available in 93% of cases. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

**Hospital Delay (DTD Time)**

Both unadjusted and adjusted geometric mean DTD times were significantly longer in women than men (adjusted, 58.5 versus 54.9 minutes; *P*<0.006).

**Total Healthcare Delay (EMS Call-to-Device Time)**

Both unadjusted and adjusted geometric healthcare delays were significantly longer in women than men (adjusted, 137.2 versus 127.2 minutes; *P*<0.001).

**Total Ischemic Time (Symptom-to-Device Time)**

Both unadjusted and adjusted geometric total ischemic times were significantly longer in women than men (adjusted, 207.0 versus 190.5 minutes; *P*<0.001).

Guideline-recommended times achieved are displayed in Figure 4.

**FMC-to-ECG Time**

Equal proportions of female and male patients with STEMI achieved an FMC-to-ECG time ≤10 minutes<sup>2</sup> (85.1% versus 85.6%; *P*=0.62).

**FMC-to-Device Time**

The percentage of female patients who were transported to a PCI-capable facility achieving a FMC-to-device time of ≤90 minutes<sup>4</sup> was 20.2% compared with 27.6% of male patients (*P*<0001).

**Clinical Outcomes**

shows the 30-day clinical outcomes. Female patients compared with male patients had higher unadjusted 30-day major adverse cardiovascular events (12.0% versus 9.1%), all-cause mortality (9.8% versus 6.7%), major adverse cardiovascular and cerebrovascular events (12.5% versus 9.6%), major bleeding (3.8% versus 2.2%), new heart failure (2.2% versus 1.4%), and new renal impairment (8.1% versus 6.0%). After

**Table 2. Ambulance Data According to Sex**

	Total Patients, n=6330	Female Patients, n=1315	Male Patients, n=5015	P Value
Prehospital ECG notification	4080 (64.5)	814 (61.9)	3266 (65.1)	0.032
Ambulance transport to non-PCI-capable hospital	939 (14.8)	194 (14.8)	745 (14.9)	0.93
Unit skill set				
MICA, 2013–2015	1687/2252 (74.9)*	335/467 (71.7)*	1352/1785 (75.7)*	0.062
MICA, 2016–2018	1805/4078 (44.2)*	350/848 (41.2)*	1455/3230 (45.0)*	0.052

Data are presented as number (percentage). MICA indicates mobile intensive care ambulance; and PCI, percutaneous coronary intervention.

\*Number of patients transported by MICA/total patients, in each respective time period.

adjustment for confounders, 30-day all-cause mortality (OR, 1.38; 95% CI, 1.06–1.79;  $P=0.02$ ) and major bleeding (OR, 1.54; 95% CI, 1.08–2.20;  $P=0.02$ ) were higher in women versus men.

## DISCUSSION

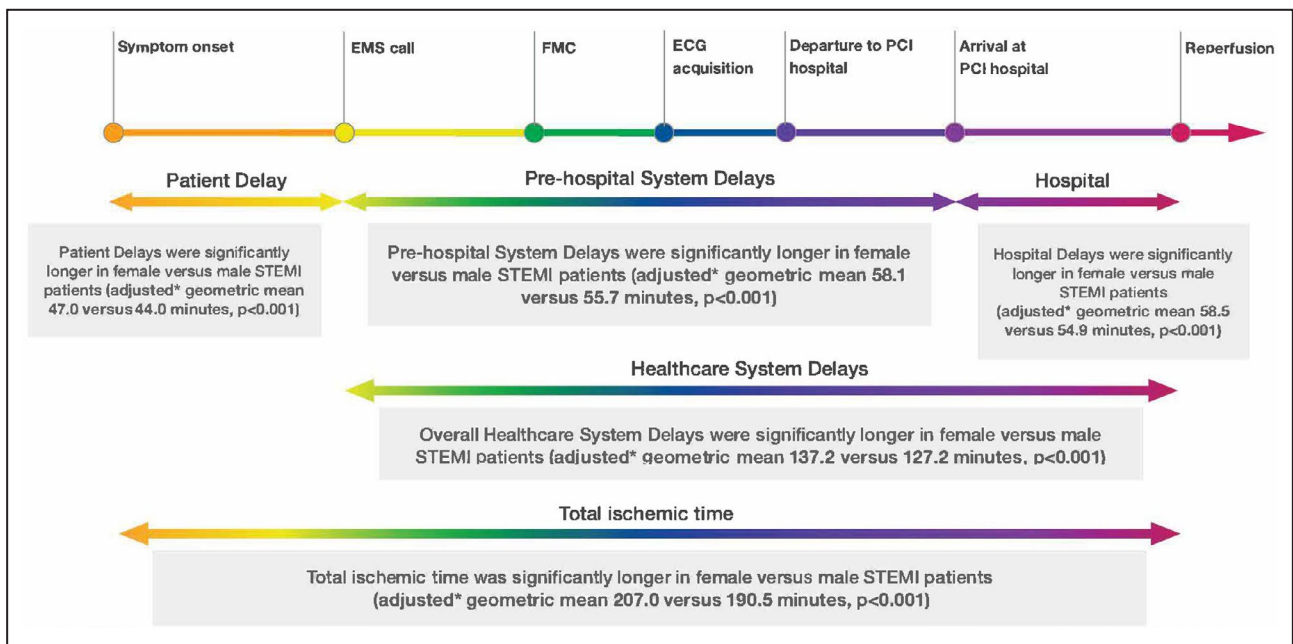
The present study investigated differences in time delays in female versus male patients presenting with

**Table 3. Geometric Mean Time Delays According to Sex\***

	Number	Geometric Mean Unadjusted	95% CI	P Value	Geometric Mean Adjusted	95% CI	P Value
Symptom-to-call time, min							
Female patients	1315	51.7	47.7–56.0	<0.001	47.0	43.0–51.3	<0.001
Male patients	5015	45.9	44.1–47.8		44.0	41.7–46.4	
Call-to-door time, min							
Female patients	1315	61.3	60.1–62.5	<0.001	58.1	56.9–59.4	<0.001
Male patients	5015	58.0	57.4–59.0		55.7	55.0–56.4	
Call-to-FMC time, min							
Female patients	1315	12.0	11.6–12.4	<0.001	11.6	11.2–12.0	0.01
Male patients	5015	11.2	11.0–11.4		11.0	10.8–11.3	
FMC-to-ECG time, min							
Female patients	1315	4.03	3.82–4.23	0.06	3.98	3.77–4.21	0.48
Male patients	5015	3.82	3.72–3.92		3.90	3.77–4.21	
ECG-to-departure time, min							
Female patients	1315	20.18	19.37–21.03	<0.001	18.32	17.53–19.15	0.002
Male patients	5015	18.49	18.10–18.88		17.05	16.59–17.52	
Total scene time, min							
Female patients	1315	24.3	23.6–25.1	<0.001	22.2	21.5–23.0	<0.001
Male patients	5015	22.4	22.0–22.8		20.8	20.4–21.3	
Departure-to-door time, min							
Female patients	1315	18.5	17.9–19.2	0.59	18.5	17.9–18.8	0.68
Male patients	5015	18.3	18.0–18.7		18.3	17.8–19.2	
Door-to-device time, min*							
Female patients	1121	68.2	65.5–70.1	<0.001	58.5	56.0–61.2	0.006
Male patients	4270	61.7	60.4–62.3		54.9	53.4–56.4	
Call-to-device time, min*							
Female patients	1121	152.5	148.0–157.2	<0.001	137.2	132.8–141.8	<0.001
Male patients	4270	136.3	134.2–138.4		127.2	124.6–129.8	
Total ischemic time*							
Female patients	1121	231.3	223.7–239.2	<0.001	207.00	199.5–214.7	<0.001
Male patients	4270	205.0	201.5–208.6		190.52	186.3–194.9	

Adjusted for age, diabetes mellitus, previous coronary artery bypass grafting and/or percutaneous coronary intervention, peripheral vascular and/or cerebrovascular disease, time of symptom onset (categorized as shown) and cardiogenic shock. Values are exponentiated regression coefficients. Adjusted values are for population mean age (62.9 years). FMC indicates first medical contact.

\*Only in patients who were initially transported to a percutaneous coronary intervention-capable hospital.



**Figure 3. Sex discrepancies in patient, prehospital, and hospital reperfusion delays in patients with STEMI transported by EMS.**

All unadjusted and adjusted geometric means for patient delays, prehospital system delays, and hospital delays were significantly longer in women than men. EMS indicates emergency medical services; FMC, first medical contact; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction. \*Adjusted for age, diabetes mellitus, estimated glomerular filtration rate, previous PCI/coronary artery bypass grafting, history of peripheral vascular disease and cerebrovascular disease, left ventricular ejection fraction, cardiogenic shock or out-of-hospital cardiac arrest requiring intubation, and occurrence time of symptom onset (day vs night).

STEMI transported to hospital by EMS. The principal findings of our study are that female patients with STEMI (1) have longer patient delays, prehospital healthcare delays, hospital delays, and total healthcare delays compared with male patients with STEMI; (2) have time delays that persisted after adjustment for confounders; (3) have two thirds of the total delays resulting from healthcare delays (female patients with STEMI experienced an adjusted excess healthcare system delay of 10 minutes compared with men); and (4) have higher 30-day all-cause mortality and major bleeding after adjustment for confounders.

Timely revascularization is of critical importance in patients with STEMI. Women are reported to experience delays in revascularization; however, different results have been published as to from where these delays arise.<sup>12–14,25,26</sup> Delays can occur at any stage from symptom onset until definitive treatment is performed and can include patient delays and healthcare system delays. As far as we are aware, our publication is the first to investigate sex differences in all time intervals from EMS call to arrival at the hospital door and subsequent PCI.

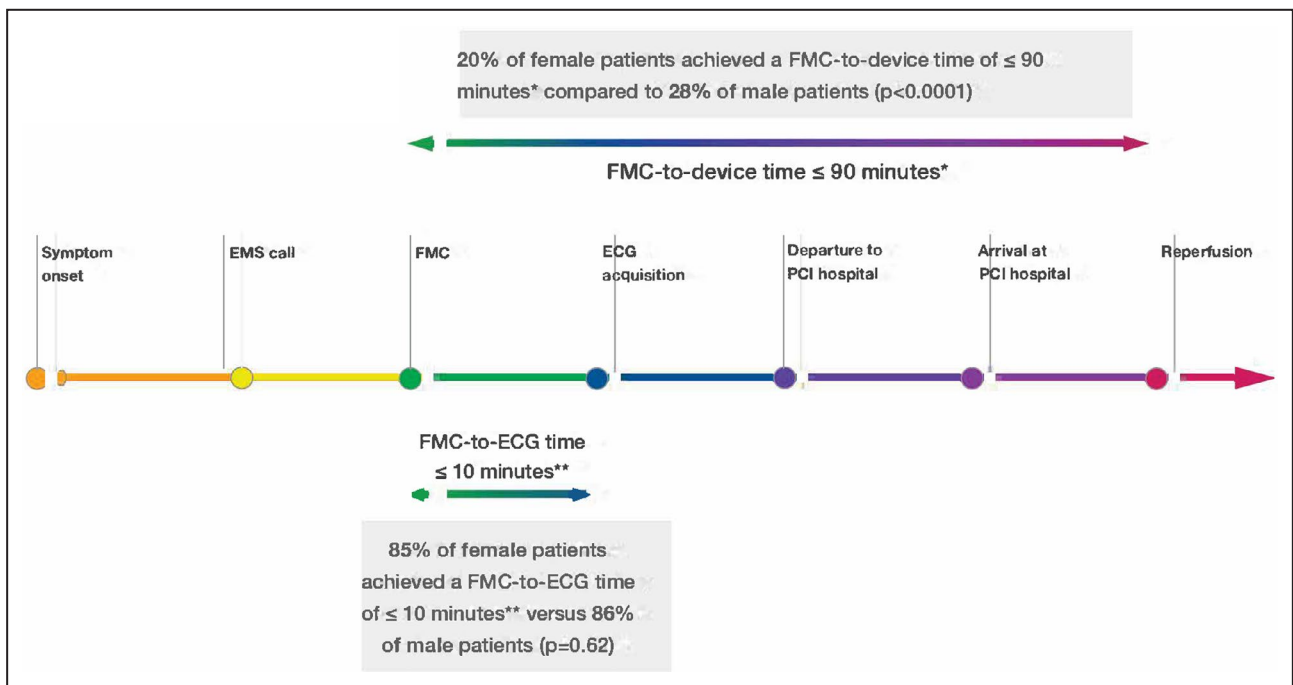
### Sources of Delay

Our STEMI cohort consisted of 21% female patients who were older and had more comorbidities

compared with male patients. We found that female patients experienced delays compared with male patients at most stages from symptom onset to revascularization. Previous studies had reported that the driver for female patients' longer ischemic times was the patient delay itself.<sup>13,14,25</sup> Our results confirm that female patients experience significant delays from time of symptom onset to calling EMS despite more women ultimately using EMS transport than men. Female patients may misinterpret their symptoms as noncardiac or not visit a healthcare provider because of engagements in caregiver roles.<sup>26,27</sup> Further causes are lower socioeconomic status of women with associated lower risk perception for heart disease as well as gender issues.<sup>27,28</sup> Comparison of time intervals to other literature is difficult because our patient cohort only included patients who were transported by EMS. This means that women in our cohort were more likely to consider their symptoms as suspicious, prompting the call of EMS.

Although patient delays are important, we found that the largest component of time delay in women with STEMI was actually healthcare system delays (prehospital system and hospital delays). In fact, only 20% of women achieved a FMC-to-device time of ≤90 minutes. Although hospital delays in women are known, significant delays in women transported by





**Figure 4. Sex discrepancies in achieved guideline-recommended times.**

The achieved guideline-recommended times are outlined. The percentage of female patients who were transported to a PCI-capable facility achieving a first medical contact-to-device time of  $\leq 90$  minutes was 20.2% compared with 27.6% of male patients ( $P<0.0001$ ). EMS indicates emergency medical services; FMC, first medical contact; and PCI, percutaneous coronary intervention. \*According to American Heart Association/American College of Cardiology guidelines.<sup>4</sup> \*\*According to European Society of Cardiology guidelines.<sup>2</sup>

EMS have not been previously described. We know that female patients with myocardial infarction have higher rates of associated symptoms such as nausea, radiation of pain, and shortness of breath.<sup>26,29</sup> Healthcare providers have also been shown to be less likely to attribute women’s symptoms to a STEMI compared with men.<sup>26,27,30</sup> This may lead to an initial misdiagnosis at the time of EMS phone call and the delay in EMS call-to-FMC seen in women. However, longer healthcare delays have been described even in women with typical symptoms, suggesting a

healthcare worker bias may still exist with women perceived as lower risk for STEMI.<sup>27</sup> Interestingly, the FMC-to-ECG time was similar between male and female patients with STEMI, an observation that has been previously described.<sup>26</sup> Of both female and male patients with STEMI, 85% achieved a FMC-to-ECG time of  $\leq 10$  minutes. This is not surprising given that EMS paramedics are highly trained and work according to clinical practice guidelines,<sup>31</sup> which have been demonstrated to reduce or even avoid sex discrepancies in treatments.<sup>32</sup>

**Table 4. Adjusted and Unadjusted Outcomes According to Sex**

30-Day Outcomes	Overall STEMI (n=6330)	Female Patients (n=1315)	Male Patients (n=5015)	Unadjusted P Value	Odds Ratio	95% CI	Adjusted* P Value
MACE	615 (9.7)	158 (12.0)	457 (9.1)	0.002	1.2	0.96–1.50	0.11
All-cause mortality	464 (7.3)	129 (9.8)	335 (6.7)	<0.001	1.38	1.06–1.79	0.02
MACCE	646 (10.2)	165 (12.5)	481 (9.6)	0.002	1.2	0.96–1.49	0.11
Major bleeding	158 (2.5)	50 (3.8)	108 (2.2)	<0.001	1.54	1.08–2.20	0.02
New heart failure	101 (1.6)	29 (2.2)	72 (1.4)	0.047	1.28	0.82–2.01	0.28
Recurrent MI	89 (1.4)	22 (1.7)	67 (1.3)	0.36	1.15	0.70–1.89	0.58
New renal impairment	394 (6.4)	103 (8.1)	291 (6.0)	0.005	1.12	0.88–1.44	0.36

Data are presented as number (percentage). MACCE indicates major cardiovascular and cerebrovascular events; MACE, major cardiovascular events; MI, myocardial infarction; and STEMI, ST-segment–elevation myocardial infarction.

\*Adjustment was made for patient age, comorbidities, cardiogenic shock, intubation and out-of-hospital cardiac arrest, and time of symptom onset (day vs night).

The ECG-to-departure time was again significantly longer in female compared with male patients. This is unexpected given the fact that female and male patients were equally as often transported by mobile intensive care ambulance and advanced life support EMS, and hence the opportunity to diagnose a STEMI at the scene was similar in both women and men. However, the detection of a STEMI pattern on the ECG may be more challenging in women because of the lower baseline J-point elevation in healthy women compared with men, leading to less-prominent ST-segment elevation in case of a STEMI.<sup>2,33</sup> Similarly, previous literature reported reperfusion delays in women even after adjusting for the presence of more subtle ECG characteristics.<sup>34</sup>

We also found a significant difference for the hospital delay (ie, DTD time) between female and male patients. This is despite similar proportions of female and male patients transported to a PCI-capable hospital, from which we can infer that a STEMI or at least an acute coronary syndrome was suspected in all of these patients.<sup>35</sup> One explanation could be that prehospital ECG notification was lower in female patients, with prehospital ECG transmission known to be associated with shorter DTD times<sup>9,36</sup> because they can facilitate direct access to the catheterization laboratory with bypassing of the emergency department. However, this factor alone is unlikely to account for the delay in women, with a previous study demonstrating female patients had longer FMC-to-device times than men, regardless of prehospital ECG transmission.<sup>16</sup>

## Ways to Improve Revascularization Delays in Women

First, we must continue to increase female patients' awareness of their risk of cardiovascular disease and the possible symptoms of a heart attack with public campaigns. More so, we have to increase healthcare providers' awareness for the likelihood of STEMI in female patients, particularly in the setting of atypical or associated symptoms and more subtle ECG findings. Education of healthcare professionals on the role of sex bias should extend from the call center provider responding to the emergency call to the interventional cardiologist activating the emergency cardiac catheterization team. Checklist-based approaches are known to reduce sex gaps in the treatment of STEMI and should be incorporated at different stages.<sup>32</sup> Artificial intelligence and machine learning could also contribute to reducing implicit bias originating from healthcare providers.<sup>37</sup>

## Limitations

Our study has certain limitations. First, this is a retrospective analysis and despite correcting for potential

confounders, only variables that are included in the registry can be adjusted for. Second, our registry only captures patients with STEMI treated with PCI, hence we cannot comment on sex differences of patients with STEMI who do not undergo revascularization, and therefore cannot exclude selection and survivor bias. However, it is well known that women with STEMI are less likely to undergo PCI,<sup>38</sup> which would only strengthen our results because patients with STEMI not taken to the catheterization laboratory are likely to have an even poorer outcome. Furthermore, only patients who were transported by Ambulance Victoria were included in the data analysis; therefore, we cannot comment on prehospital time discrepancies in all-comer patients with STEMI. However, data on that have previously been published,<sup>13</sup> and the intention of this work was to specifically analyze a homogeneous cohort of patients who were transported by EMS with regard to prehospital healthcare system delays.

## CONCLUSIONS

In conclusion, despite guideline-based assessment and treatment pathways through EMS, there are still sex discrepancies with significant patient, prehospital, and hospital reperfusion delays in female patients with STEMI. This likely represents a complex construct of differences in symptoms and ECG changes as well as patient and professional bias, which all require specific strategies to address.

## ARTICLE INFORMATION

Received February 18, 2021; accepted April 21, 2021.

### Affiliations

School of Clinical Sciences at Monash Health, Monash Cardiovascular Research Centre (J.S., S.Z.), Centre of Cardiovascular Research and Education in Therapeutics, School of Public Health and Preventive Medicine (D.D., S.J.D., A.B., J.L., D.S.) and Department Epidemiology and Preventive Medicine (K.S., E.A., Z.N.), Monash University, Melbourne, Australia; Department of General Medicine (M.D.) and Department of Cardiology (S.J.D., D.S.), The Alfred Hospital, Melbourne, Australia; Centre for Research and Evaluation, Ambulance Victoria, Melbourne, Australia (K.S., E.A., Z.N., C.M.R., D.S.); School of Public Health, Curtin University, Perth, Australia (C.M.R.); Department of Cardiology, Royal Melbourne Hospital, Melbourne, Australia (J.L.); Baker Heart and Diabetes Institute, Melbourne, Australia (S.J.D., D.S.); Department of Cardiology, Westmead Hospital, Sydney, Australia (S.Z.); and Westmead Applied Research Centre, University of Sydney, Australia (S.Z.).

### Sources of Funding

None.

### Disclosures

Dr Stehli is supported by a Monash University Scholarship. Associate Professor Stub receives a National Heart Foundation Fellowship. Associate Professor Duffy is supported by a National Health and Medical Research Council of Australia grant (No. 1111170). Associate Professor Zaman is supported by a National Heart Foundation Fellowship. She has also obtained research funding from Abbott Vascular and Biotronik Australia and speaking honoraria or consulting fees from AstraZeneca, Amgen, and Medtronic Australia. Dr Nehme is supported by a National Health and Medical Research Council Early Career Fellowship (No. 1146809). The remaining authors have no disclosures to report.

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