

Impact of Sex and Contact-to-Device Time on Clinical Outcomes in Acute ST-Segment Elevation Myocardial Infarction—Findings From the National Cardiovascular Data Registry

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Background—Emergent myocardial reperfusion via primary percutaneous coronary intervention is optimal care for patients presenting with ST-segment elevation myocardial infarction (STEMI). Delays in such interventions are associated with increases in mortality. With the shift in focus to contact-to-device (C2D) time as a new perfusion metric, this study was designed to examine how sex affects C2D time and mortality in STEMI patients.

Methods and Results—Clinical data on male and female STEMI patients were extracted and analyzed from the National Cardiovascular Data Registry from July 1, 2008 to December 31, 2014. A total of 102 515 patients were included in the final analytic cohort. The median C2D time in female patients with STEMI was delayed when compared to male patients (80 [65–97] versus 75 [61–90] minutes; $P < 0.001$). The unadjusted mortality was higher in female patients when compared to male patients with STEMI (4.1% versus 2.0%; $P < 0.001$). For every 5-minute increase in C2D time, the adjusted odds ratio for mortality was 1.04 (95% CI, 1.03–1.06) for female patients with STEMI and 1.07 (95% CI, 1.06–1.09) for male patients (P for sex by C2D interaction = 0.003).

Conclusions—To date, this is the largest analysis of STEMI patients that measures the impact of the new recommended C2D reperfusion metric on in-hospital mortality. Female STEMI patients have longer C2D times and increased mortality. The disparity can be improved and survival can increase in this high-risk patient cohort by decreasing systems issues that cause increased reperfusion times in female STEMI patients. (*J Am Heart Assoc.* 2017;6:e004521. DOI: 10.1161/JAHA.116.004521.)

Key Words: disparities • mortality • reperfusion • sex-specific • ST-segment elevation myocardial infarction

Emergent myocardial reperfusion via primary percutaneous coronary intervention (PCI) is considered optimal care for patients presenting acutely with ST-segment elevation myocardial infarction (STEMI).¹ It has been shown that

delay in such an intervention is associated with significant increases in mortality.² Various metrics have been proposed in order to predict index hospitalization and long-term outcomes. The end point of this intervention is restoration of coronary blood flow. In the past, there had been a focus on achieving a door-to-balloon (D2B) time ≤ 90 minutes, ie, time of hospital arrival to primary PCI.³ D2B time has proven to be a fair metric, and strategies such as prehospital transmission of ECGs have been designed around meeting such a benchmark with moderate success.^{4–7} Studies have shown that reducing D2B times beyond this 90-minute benchmark has not resulted in decreased mortality; notably, mortality from STEMI has plateaued with further reductions in D2B. Menees et al⁸ have demonstrated a 20% reduction in D2B times from 83 minutes in 2005, with no effect on mortality.

In 2013, the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) updated their guidelines with a new focus and terminology. The proposed guidelines suggested a switch from D2B time to the time of first medical contact, be that at a doctor's office, at home, or in the field, to the time of restoration of coronary blood flow by any reperfusion device. Reperfusion devices include

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An accompanying Data S1 is available at <http://jaha.ahajournals.org/content/6/1/e004521/DC1/embed/inline-supplementary-material-1.pdf>

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balloons, coronary stents, wires, aspiration catheters, and other devices used to restore impeded blood flow. This shift changed the focus to include prehospital STEMI care including onsite clinical assessments and transportation to an emergency facility. Furthermore, the guidelines suggested that this contact-to-device (C2D) time be ≤ 90 minutes in order to achieve optimal patient outcomes.¹

Population disparities have long existed in STEMI patients, and it has been shown that females are less likely to receive primary PCI when compared to males.^{9–11} Furthermore, female patients tend to have longer D2B times than their male counterparts.¹² In 2006, the ACC launched the D2B Alliance, which focused on standardized systematic approaches to STEMI patients and ultimately reduced D2B times and created more parity in reperfusion times related to sex.^{6,13–15} The effects of prehospital care and subsequent D2B time, which are captured by C2D times, have not been previously analyzed to explore the association with mortality and potential sex-linked disparities. The examination of prehospital and emergency care for STEMI patients is a novel approach as strategies for lessening total ischemic time are being proposed. This has a high potential impact by providing insight into prehospital care and its impact on mortality in STEMI patients. The primary aim of this study is to examine the newly proposed C2D time in STEMI patients as it relates to sex. The secondary aim is to compare mortality and C2D time in STEMI patients stratified by sex, prehospital ECG, and mode of transportation to the hospital.

Methods

Data Source

This study utilized the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry-Get with the Guidelines (ACTION Registry-GWTG) database. The ACTION Registry-GWTG is a nationwide, ongoing, voluntary quality improvement initiative of the American College of Cardiology and the AHA, with partnering support from the Society of Cardiovascular Patient Care and the American College of Emergency Physicians. The ACTION Registry-GWTG contains baseline and in-hospital data on high-risk patients who are hospitalized with STEMI and non-STEMI. Details of the design and conduct of the registry have been previously described.^{16,17} Standardized data collection includes patient demographics, medical history, and in-hospital clinical processes of care and outcomes. The validity of data collection in the ACTION Registry-GWTG has been reported.¹⁷ During January 1, 2007, to December 31, 2014, there were 1083 sites that furnished data to the ACTION Registry-GWTG database. STEMI was defined clinically as new or presumed new sustained ST-segment elevation at the J

point in two contiguous ECG leads with the cutoff points ≥ 2 mm in male patients or ≥ 1.5 mm in female patients in leads V2 or V3 and/or ≥ 1 mm in other leads and lasting ≥ 20 minutes or new left bundle branch block with associated symptoms characteristic of myocardial ischemia.

In the ACTION Registry-GWTG, the time and date of first evaluation by emergency medical services (EMS) and patient arrival to an ACTION Registry-GWTG hospital was collected. Furthermore, the time and date of first device activation was also collected. Device activation was measured as the earliest time when any reperfusion device had restored coronary blood flow. C2D time was calculated by subtracting the first medical contact time noted from the time that blood flow down a coronary artery was restored. The symptom to onset time was calculated by subtracting the reported symptom onset time from the first medical contact time noted.

Patient Population

Starting July 1, 2008, first medical contact times were available, which allowed calculation of the new perfusion metric, C2D time. Data were available for 257 197 patients in the study period July 1, 2008, to December 31, 2014, at 825 sites in the United States who presented with STEMI. An attempt was made to study a patient population with limited confounders. Hospitals without surgical capabilities may or may not perform elective PCI depending on their location. To minimize potential confounders in the analysis of outcomes, patients from hospitals without surgical capabilities were excluded. In the data set, $>97\%$ of STEMI patients traveled via ambulance or presented as walk-in patients to the hospital. The patients who traveled via air and mobile intensive care units were excluded as their reperfusion times significantly differed from most patients in the data set. Patients with incomplete data such as unknown mode of transportation and missing location of first ECG were excluded from the analysis. To further limit confounders, patients who did not undergo primary PCI were excluded. Examples include but are not limited to patients who received thrombolysis and then rescue PCI and interhospital transfers. If the patient met STEMI criteria for the National Cardiovascular Data Registry but the provider did not think the patient clinically was having a STEMI, these patients were excluded as C2D time and time to undergo PCI would extend beyond 12 hours. Patients with nonsystem reasons for delay in PCI such as difficulty in obtaining consent were also excluded to limit confounders. Ultimately, the population studied included 102 515 patients at 760 sites (Figure 1).

Statistical Analysis

The following data were stratified by sex for analysis: patient baseline demographics, cardiac status on first medical

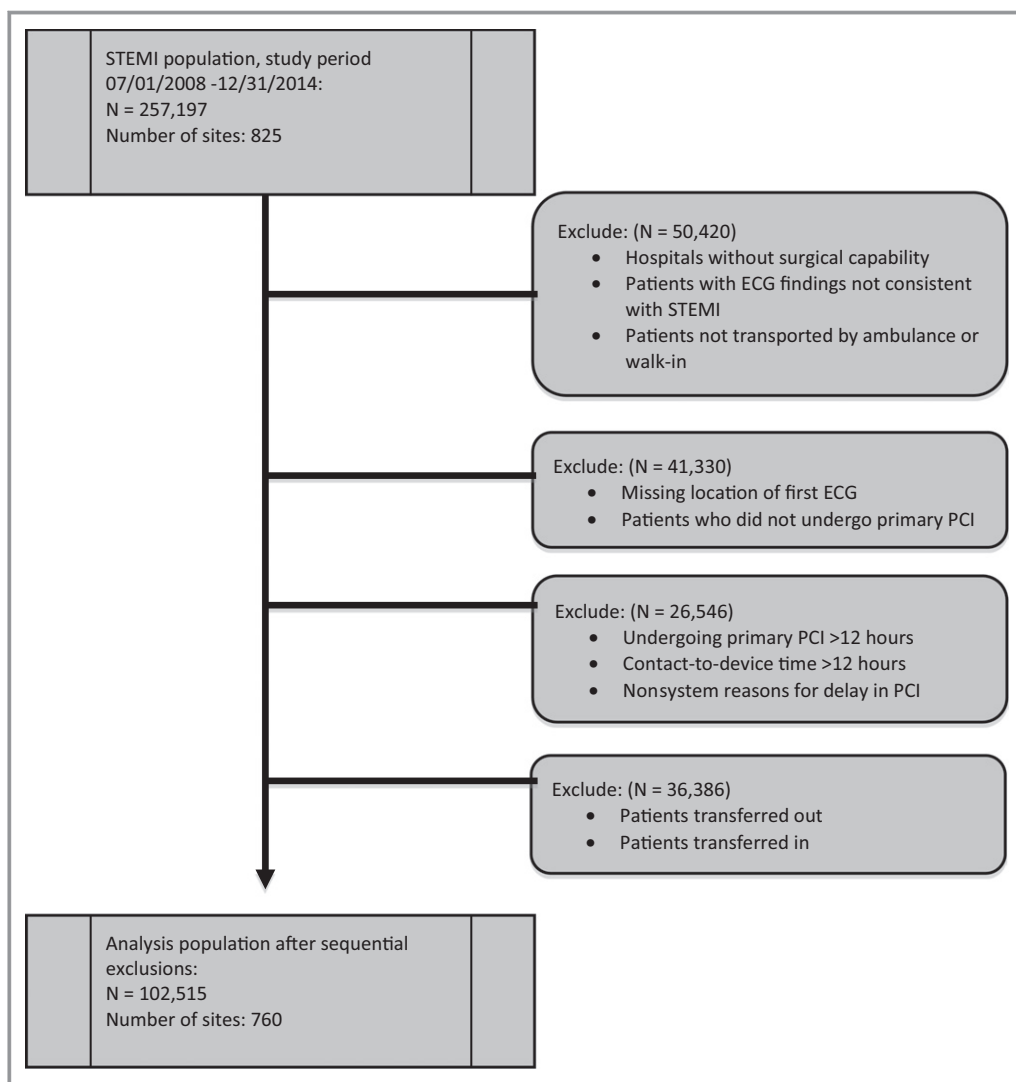


Figure 1. Patient flow. Please note that the exclusions are not all mutually exclusive. STEMI indicates ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

contact, medical history, mode of transportation, in-hospital clinical events including mortality, in-hospital laboratory results, home medications, and medications given during the index hospitalization. Data regarding reperfusion times, including C2D time, were stratified by sex, mode of transportation to the providing facility, and prehospital ECG transmission. Differences between female and male STEMI patients were compared using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables.

Logistic regression generalized estimating equations were used to assess the relationship between in-hospital mortality and C2D time. The logistic generalized estimating method uses an exchangeable working correlation matrix to account for within-hospital clustering of patient-level factors. This approach produced estimates that are similar to those from logistic regression with variances that are adjusted for the

correlation of outcomes within a hospital.¹⁸ Although this working correlation structure assumes that hospitals are independent after adjusting for covariates, empirical standard error estimates for inference were used, which provide robustness against possible misspecification of the correlation structure. Linearity for C2D time with respect to log odds of in-hospital mortality was checked. The model consisted of a list of patient covariates from the previously validated ACTION Registry–GWTG in-hospital mortality (Data S1).¹⁹ These included demographics, medical comorbidities, signs and symptoms at presentation, relevant laboratory results, home medications, insurance status, mode of transportation, use of prehospital ECG, and time from symptom onset to first medical contact. These covariates were included for the purpose of adjusting for a potential imbalance in risk factors. With sex and C2D time in the model, age and comorbidities (hypertension, current/recent smoker, diabetes mellitus,

dyslipidemia, prior PCI, prior coronary artery bypass graft surgery, prior heart failure, prior stroke, prior peripheral arterial disease, heart failure, and cardiogenic shock) remained statistically significant at the $P<0.05$ level in the model. Furthermore, interaction between C2D time and sex with respect to in-hospital mortality was explored. Odds ratios (ORs) and 95% CIs for mortality in C2D time were reported among female and male patients. Steps were taken to eliminate incomplete data, and, in the final analysis, about 1% of the variables had missing data. For modeling, missing values in the continuous covariates were imputed to sex-specific medians of the nonmissing values. For categorical variables, missing values were imputed to the most frequent groups. A P value <0.05 was considered statistically significant for all analyses. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Demographics and Comorbidities

In the analytic cohort, 27.2% of the STEMI patients were female. Female patients with STEMI had a higher median (25th–75th percentiles) age than their male counterparts (64 [55–75] versus 58 [51–66] years) (Table 1) and a higher percentage of female patients were enrolled in Medicare compared to male patients. Female STEMI patients also presented with a higher incidence of comorbidities compared to male patients including higher rates of hypertension, chronic lung disease, diabetes mellitus, prior stroke, and peripheral artery disease. Male patients had higher rates of prior myocardial infarction and revascularization than female patients (Table 1).

Mode of Transportation and Clinical Data

In this cohort, male and female patients with STEMI both presented to STEMI centers that utilized prehospital ECG transmissions at roughly equivalent rates (Table 1). Approximately 61.5% of the STEMI patients arrived to the hospital via ambulance. Female patients alerted EMS more than male patients and arrived more often in an ambulance (65.9% versus 59.8%). However, in all patients arriving via EMS, 70.9% of female patients with STEMI had prehospital ECG transmitted to their receiving hospitals compared with 73.9% of male patients.

There was a higher incidence of shock and heart failure noted on first medical contact in female patients with STEMI. The median initial hemoglobin level was lower on admission in the female population as was the median initial glomerular filtration rate calculated by the Cockcroft-Gault formula (Table 1).

Medication Use During the Index Hospitalization

More than 99% of all patients received aspirin within 24 hours of their index hospitalization (Table 2). Female STEMI patients received clopidogrel within 24 hours more often than male STEMI patients who more often received the novel thienopyridine, prasugrel. Bivalirudin was administered equally to patients in the database (female patients 46.8% versus male patients 46.7%), but intravenous glycoprotein IIa/IIIb inhibitors were used more frequently in male patients with STEMI.

Reperfusion Times

Female STEMI patients had longer reperfusion times when compared to male patients. The goal of arrival to ECG ≤ 10 minutes was reached in 75.4% of female patients compared to 82.5% of male patients in the population. The median (25th–75th percentiles) C2D times in female patients with STEMI were delayed when compared to male patients (80 [65–97] versus 75 [61–90] minutes; $P<0.001$) (Figure 2). Female patients also had longer C2D times than male patients regardless of the mode of transportation and prehospital ECG transmission (Figure 3). The majority of female patients with STEMI in the study presented by ambulance with prehospital ECG transmission, and the C2D time in that specific mode of transportation was delayed compared to male patients (83 [69–99] versus 79 [65–94] minutes; $P<0.001$) (Figure 3). Female STEMI patients also less frequently achieved the target C2D ≤ 90 minutes than male patients (67.5% versus 75.6%; $P<0.001$).

Prehospital times were also prolonged in female patients in the database. Female patients with STEMI had longer symptom onset to first medical contact times compared to the male patients in the cohort (75 [34–186] versus 63 [31–150] minutes; $P<0.001$). Given delayed prehospital times and delayed C2D times, female patients with STEMI had longer total ischemic times when compared to male STEMI patients (161 [117–270] versus 145 [108–229] minutes; $P<0.001$).

In-Hospital Clinical Events and Mortality

During the index hospital, there were more statistically significant adverse clinical events in female STEMI patients when compared to male patients (Table 3). There was a higher rate of cardiogenic shock in female versus male patients (5.8% versus 4.0%; $P<0.001$) and heart failure (5.8% versus 3.4%; $P<0.001$) (Table 3).

In-hospital mortality

More female STEMI patients died in the index hospitalization when compared to male patients (4.1% versus 2.0%; $P<0.001$).

Table 1. Baseline Clinical Characteristics Stratified by Sex

Variable	Women (n=27 839)	Men (n=74 676)
Demographics		
Age, y	64 (55–75)	58 (51–66)
Ethnicity		
Caucasian, non-Hispanic	80.6	81.2
Black, non-Hispanic	12.1	8.6
Hispanic	5.0	6.6
East Asian	1.4	2.6
Other	0.4	0.4
Weight, kg	73.6 (63.5–86.7)	88.6 (78.0–101.0)
Medicare insurance	25.1	16.0
Medical history		
Diabetes mellitus	28.1	21.5
Hypertension	69.2	60.2
Current/recent smoker (<1 year)	42.4	44.5
Prior MI	15.5	19.0
Prior CABG	4.0	5.4
Prior PCI	17.5	22.1
Dyslipidemia	53.7	52.6
Currently on dialysis	1.0	0.5
Chronic lung disease	11.3	7.0
Prior heart failure	4.9	2.8
Prior stroke	5.7	3.4
Peripheral arterial disease	5.4	3.9
Home medication		
Aspirin	30.5	31.2
P2Y ₁₂ receptor inhibitor	9.3	8.7
Blocker	28.2	22.7
Statin	29.7	29.1
ACE inhibitor or ARB	32.0	26.7
Laboratory values		
Initial glycated hemoglobin, %	6.1 (5.6–7.6)	6.0 (5.6–7.1)
High-density lipoprotein, mg/dL	41 (34–50)	35 (30–43)
Low-density lipoprotein, mg/dL	103 (78–132)	101 (77–127)
Initial hemoglobin, g/dL	13.4 (12.3–14.5)	15.0 (13.9–16.0)
Initial Cockcroft-Gault estimated GFR, mL/min	75.3 (52.5–103.9)	95.3 (73.8–102.8)

Continued

Table 1. Continued

Variable	Women (n=27 839)	Men (n=74 676)
Cardiac status on first medical contact		
Systolic blood pressure, mm Hg	139 (117–160)	142 (121–162)
Heart rate, beats per min	78 (65–92)	78 (65–91)
Heart failure	5.6	3.9
Cardiogenic shock	5.6	4.2
Cardiac arrest	2.9	3.4
Mode of transport		
Prehospital ECG	46.7	44.2
Ambulance	65.9	59.8
Self/family	34.1	40.2

Values are expressed as median (25th–75th percentiles) or percentage. All variables are statistically significant at the $P<0.01$ level, except for aspirin and statins. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.

(Table 3). Analysis of the data revealed that there was a proportional increase in adjusted risk of mortality with increasing C2D time (Figure 4). For every 5-minute increase in C2D time, the adjusted OR for mortality was 1.04 (95% CI, 1.03–1.06) for female patients with STEMI and 1.07 (1.06–1.09) for male patients (P for sex by C2D interaction=0.003). For delayed C2D time >90-minute benchmark, the OR for mortality was 1.28 (1.12–1.45) in female patients and 1.69 (1.51–1.90) in male patients with STEMI (P for sex by C2D interaction=0.001).

Discussion

The median C2D time in female patients is longer than male patients, and female patients with STEMI also experience delays in crucial admission procedures such as arrival to ECG times. Regardless of the mode of transportation to the hospital and prehospital ECG transmission for STEMI, female patients have delayed times when compared to male patients (Figure 3).

There are several proposed reasons female patients have delayed C2D times when compared to male patients. Both male and female patients tend to reason that their chest pain will be self-limiting and that they would rather not burden others with their medical issues, especially if it turns out to be non-life-threatening.^{20,21} Specifically for female patients, there is still a misperception that coronary artery disease is not a major health problem. Although more female patients die from coronary artery disease than breast cancer, breast

Table 2. In-Hospital Procedures and Treatments Stratified by Sex

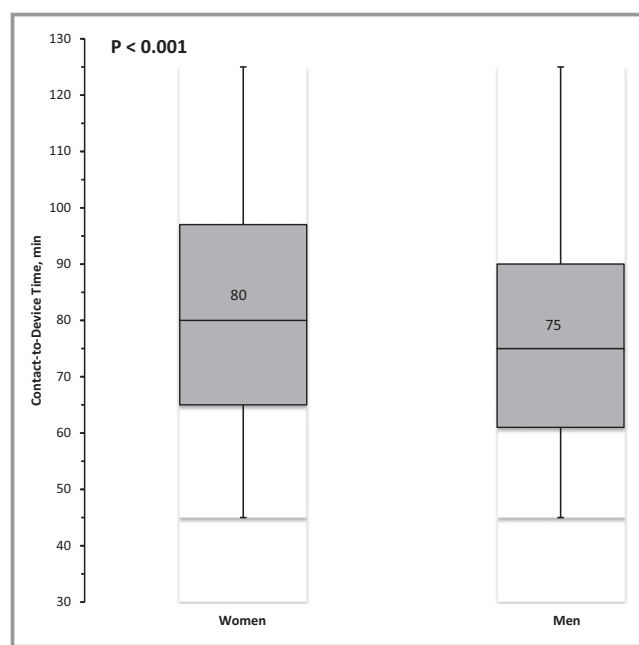
Variable, %	Women (n=27 839)	Men (n=74 676)
Diseased vessels during catheterization		
One	42.7	39.2
Two	33.2	34.0
Three	23.4	26.1
Left ventricular ejection fraction		
>50%	58.0	54.2
40% to 50%	22.9	26.0
25% to 40%	16.1	16.4
<25%	2.7	3.0
Medications within first 24 hours of the index hospitalization*		
Aspirin	99.0	99.2
Clopidogrel	68.7	62.2
Prasugrel	22.9	31.7
Blocker	89.7	91.0
ACE inhibitor or ARB	52.9	56.7
Statin	77.8	81.3
Anticoagulants/IV antiplatelet agents anytime during the index hospitalization*		
Glycoprotein IIb/IIIa inhibitor	54.2	58.1
IV unfractionated heparin	69.8	71.0
Bivalirudin	46.8	46.7
Low molecular weight heparin	12.3	11.9
Fondaparinux	0.2	0.2

All variables are statistically significant at the $P < 0.01$ level, except for aspirin, bivalirudin, low molecular weight heparin, and fondaparinux. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IV, intravenous.

*Patients in whom these medications were contraindicated were excluded.

cancer is perceived as the major health issue facing this population.²² This misperception that female patients do not have coronary artery disease can translate into delayed prehospital assessment that delays C2D times.

From prior studies, it is known that female patients wait longer to activate EMS during a STEMI.^{23,24} Results from the analysis corroborate those data as female patients have longer symptom onset to contact times when compared to male patients. Generally, patients with acute coronary syndromes are reluctant to activate EMS with symptoms of a potential acute coronary syndrome. Given that EMS is accessible to >98% of the US population, only 61.5% of the patients in this cohort utilized EMS as a mode of transportation for STEMI.¹ This aligns with prior studies showing that 60% of STEMI patients use EMS.²⁵ Results of this analysis show that more female patients were transported to emergency facilities by EMS than male patients. When patients

**Figure 2.** Contact-to-device time in men and women.

with STEMI are transported to their receiving hospitals by EMS and a prehospital ECG is transmitted to that hospital, the odds increase of achieving target C2D time ≤ 90 minutes.⁷ In this cohort, female and male patients had similar prehospital ECG transmission rates in part because male patients used EMS less than female patients. When parsing the data in the EMS-only cohort, prehospital ECGs for female patients with STEMI are transmitted proportionately less than male patients, thus decreasing the odds of female patients reaching a C2D time ≤ 90 minutes. The arrival to ECG time is also increased in female patients when prehospital ECGs are not used.

In addition, observed in-hospital unadjusted mortality in female patients with STEMI was twice that of their male counterparts in this study (Table 3). Female STEMI patients generally present at a more advanced age and with more comorbid conditions such as diabetes mellitus and hypertension (Table 1). These risk factors may contribute to higher mortality with STEMI. Female sex is known to be an independent predictor of in-hospital mortality even after adjusting for these variables.²⁶ Although attention needs to be focused on reducing reperfusion times, further research needs to be performed to explore other contributing factors that augment the risk of mortality in female patients when C2D times are comparable between the sexes, such as: (1) investigating preventive strategies to reduce comorbidities in female patients who present with STEMI; (2) analyzing the effectiveness of treatments for comorbid conditions in female STEMI patients, and (3) examining the impact of sex-based adverse effects of standard treatments for STEMI, which can impact mortality.

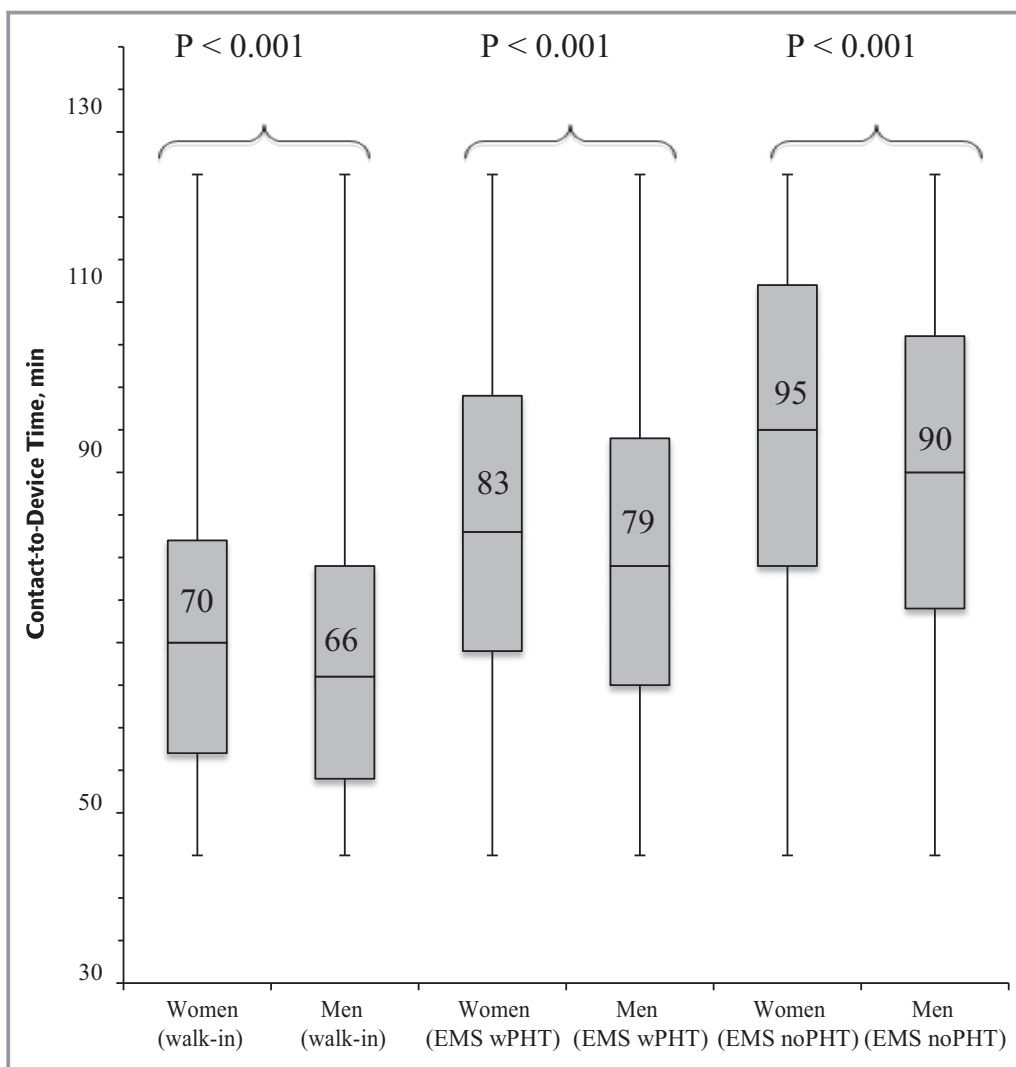


Figure 3. Contact-to-device times stratified by sex and mode of transportation. EMS indicates emergency medical services; PHT, prehospital transmission of ECG.

Although female STEMI patients present with more comorbidities, there are possible interventions that could reduce mortality rates in female patients with STEMI, such as decreasing reperfusion times. Female patients with STEMI have higher adjusted mortality than male patients and their ischemic time is longer at every step of their medical care.

Table 3. In-Hospital Clinical Events Stratified by Sex

Variable, %	Women (n=27 839)	Men (n=74 676)	P Value
Death	4.1	2.0	<0.001
Heart failure	5.8	3.4	<0.001
Cardiogenic shock	5.8	4.0	<0.001
Stroke	0.8	0.3	<0.001
Cardiac arrest	4.4	3.4	<0.001

Shorter C2D times are associated with increased adjusted survival rates in a sex-dependent fashion. For every 5-minute decrease in C2D time, there is a 4% increase in the odds of survival during hospitalization among female patients with STEMI after adjusting for patient baseline characteristics. There is a 28% increase in the odds of survival for female patients who have C2D times within the 90-minute target after adjusting for patient baseline characteristics. A total of 32.5% of female STEMI patients did not meet the ACCF/AHA–recommended target time C2D ≤90 minutes compared with 24.4% of male patients. Even at the shortest C2D times, female patients with STEMI still have higher mortality rates when compared to male patients. The adjusted mortality rate is higher in female STEMI patients even though the odds of mortality is higher in male patients with delayed C2D times.

Meenes et al⁸ have shown that further reduction in D2B times have not resulted in decreased mortality in patients

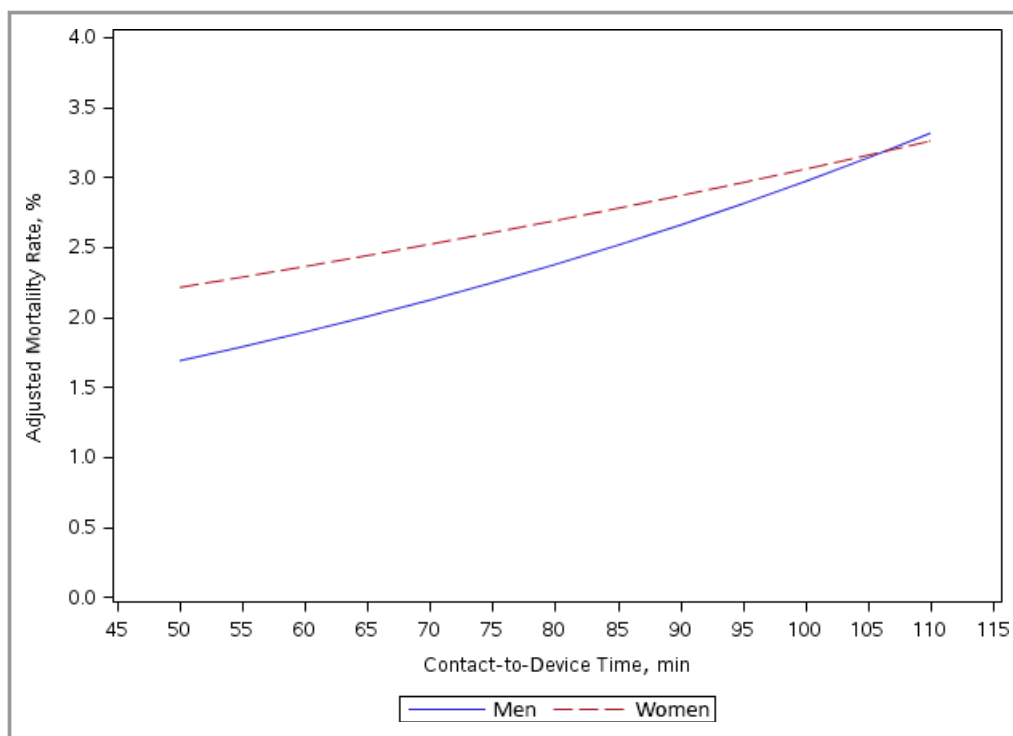


Figure 4. Logistic generalized estimating analysis exploring the relationship of contact-to-device time and mortality stratified by sex.

with STEMI. It appears that it is prudent to shift focus to prehospital care to investigate how C2D times can be shortened, which will improve survival. The primary goal should be to improve patient education about the symptoms of an acute coronary syndrome that would ultimately lessen symptom onset to contact time in patients, especially in female patients. Patients also need further guidance to use EMS for potential acute coronary syndromes, and EMS personnel should use prehospital transmission of ECGs to receiving hospitals as much as possible. In 2006, the ACC launched an initiative to focus on standardized guidelines to improve in-hospital reperfusion times.⁵ Since that launch, D2B times have drastically decreased and sex-related disparities in D2B times have improved.²⁷ A similar initiative that is focused on standardizing prehospital assessment would likely improve C2D times, mitigate disparities based on sex, and improve survival from STEMI. It is crucial that STEMI centers continue to work with EMS personnel to increase prehospital ECG transmission in female patients with STEMI, shorten transfer times to STEMI centers, and explore the reasons first medical contact time to arrival times are also delayed in female patients, which will affect survival.

Study Limitations

This study is retrospective and based on registry data and therefore includes the inherent limitations of those methods.

There was no true adjudication of the clinical events that might have affected the results. The participating hospitals in the database may not be representative of the geographical distribution of hospitals across the country and may have differing expertise in managing STEMI patients. Finally, although we attempted to address the relationship between sex and C2D time to in-hospital mortality by adjusting for a broad range of patient-level clinical factors, the possibility of confounding by unmeasured covariates remains.

Conclusions

To date, this is the largest analysis of STEMI patients stratified by sex and mode of transportation and prehospital ECG to measure the impact of the new recommended C2D reperfusion metric on in-hospital mortality. It is evident that there is a sex-based disparity in reperfusion times, in that female patients with STEMI have longer C2D times than male patients. Female STEMI patients also have increased mortality when compared to male STEMI patients, partially due to certain clinical demographics. Further investigation is needed to mitigate the sex-specific circumstances that exacerbate the risk of mortality for female STEMI patients. With continued work on decreasing prehospital systems issues that cause increased reperfusion times in female patients with STEMI, the disparity can be improved and survival can increase in this high-risk female patient cohort.

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Disclosures

None.

References

- O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
- Collins SD. Acute myocardial infarction in women: is there a sex disparity between door-to-balloon time and clinical outcomes? *Cardiovasc Revasc Med*. 2012;13:125–127.
- Kushner FG, Hand M, Smith SC Jr, King SB III, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE Jr, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2009;54:2205–2241.
- Bradley EH, Nallamothu BK, Stern AF, Cherlin EJ, Wang Y, Byrd JR, Linnander EL, Nazem AG, Brush JE Jr, Krumholz HM. The door-to-balloon alliance for quality: who joins national collaborative efforts and why? *Jt Comm J Qual Patient Saf*. 2009;35:93–99.
- Krumholz HM, Bradley EH, Nallamothu BK, Ting HH, Batchelor WB, Kline-Rogers E, Stern AF, Byrd JR, Brush JE Jr. A campaign to improve the timeliness of primary percutaneous coronary intervention: door-to-balloon: an alliance for quality. *JACC Cardiovasc Interv*. 2008;1:97–104.
- Mehta RH, Bufalino VJ, Pan W, Hernandez AF, Cannon CP, Fonarow GC, Peterson ED; American Heart Association Get With the Guidelines Investigators. Achieving rapid reperfusion with primary percutaneous coronary intervention remains a challenge: insights from American Heart Association's Get With the Guidelines program. *Am Heart J*. 2008;155:1059–1067.
- Roswell RO, Greet B, Parikh P, Mignatti A, Freese J, Lobach I, Guo Y, Keller N, Radford M, Bangalore S. From door-to-balloon time to contact-to-device time: predictors of achieving target times in patients with ST-elevation myocardial infarction. *Clin Cardiol*. 2014;37:389–394.
- Menees DS, Peterson ED, Wang Y, Curtis JP, Messenger JC, Rumsfeld JS, Gurm HS. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med*. 2013;369:901–909.
- Lawesson SS, Alfredsson J, Fredrikson M, Swahn E. A gender perspective on short- and long term mortality in ST-elevation myocardial infarction—a report from the SWEDEHEART Register. *Int J Cardiol*. 2013;168:1041–1047.
- Leurent G, Garlandezec R, Auffret V, Hacot JP, Coudert I, Filippi E, Rialan A, Moquet B, Rouault G, Gilard M, Castellant P, Druelles P, Boulanger B, Treuil J, Avez B, Bedossa M, Boulmier D, Le Guellec M, Le Breton H. Gender differences in presentation, management and inhospital outcome in patients with ST-segment elevation myocardial infarction: data from 5000 patients included in the ORBI prospective French regional registry. *Arch Cardiovasc Dis*. 2014;107:291–298.
- Radovanovic D, Nallamothu BK, Seifert B, Bertel O, Eberli F, Urban P, Pedrazzini G, Rickli H, Stauffer JC, Windecker S, Erne P; AMIS Plus Investigators. Temporal trends in treatment of ST-elevation myocardial infarction among men and women in Switzerland between 1997 and 2011. *Eur Heart J Acute Cardiovasc Care*. 2012;1:183–191.
- Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L; Get With the Guidelines Steering Committee Investigators. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118:2803–2810.
- Rezaee ME, Brown JR, Conley SM, Anderson TA, Caron RM, Niles NW. Sex disparities in pre-hospital and hospital treatment of ST-segment elevation myocardial infarction. *Hosp Pract (1995)*. 2013;41:25–33.
- Sullivan AL, Beshansky JR, Ruthazer R, Murman DH, Mader TJ, Selker HP. Factors associated with longer time to treatment for patients with suspected acute coronary syndromes: a cohort study. *Circ Cardiovasc Qual Outcomes*. 2014;7:86–94.
- Valente S, Lazzeri C, Chiostrì M, Giglioli C, Zucchini M, Grossi F, Gensini GF. Gender-related difference in ST-elevation myocardial infarction treated with primary angioplasty: a single-centre 6-year registry. *Eur J Prev Cardiol*. 2012;19:233–240.
- Peterson ED, Roe MT, Chen AY, Fonarow GC, Lytle BL, Cannon CP, Rumsfeld JS. The NCDR ACTION Registry–GWTG: transforming contemporary acute myocardial infarction clinical care. *Heart*. 2010;96:1798–1802.
- Peterson ED, Roe MT, Rumsfeld JS, Shaw RE, Brindis RG, Fonarow GC, Cannon CP. A call to ACTION (Acute Coronary Treatment and Intervention Outcomes Network): a national effort to promote timely clinical feedback and support continuous quality improvement for acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009;2:491–499.
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121–130.
- Chin CT, Chen AY, Wang TY, Alexander KP, Mathews R, Rumsfeld JS, Cannon CP, Fonarow GC, Peterson ED, Roe MT. Risk adjustment for in-hospital mortality of contemporary patients with acute myocardial infarction: the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry–Get With the Guidelines (GWTG) acute myocardial infarction mortality model and risk score. *Am Heart J*. 2011;161:113–122.e112.
- Leslie WS, Urie A, Hooper J, Morrison CE. Delay in calling for help during myocardial infarction: reasons for the delay and subsequent pattern of accessing care. *Heart*. 2000;84:137–141.
- Rucker D, Brennan T, Burstin H. Delay in seeking emergency care. *Acad Emerg Med*. 2001;8:163–169.
- Wenger NK. You've come a long way, baby: cardiovascular health and disease in women: problems and prospects. *Circulation*. 2004;109:558–560.
- Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. *Am Heart J*. 2011;161:91–97.
- Ladwig KH, Meisinger C, Hymer H, Wolf K, Heier M, von Scheidt W, Kuch B. Sex and age specific time patterns and long term time trends of pre-hospital delay of patients presenting with acute ST-segment elevation myocardial infarction. *Int J Cardiol*. 2011;152:350–355.
- Mathews R, Peterson ED, Li S, Roe MT, Glickman SW, Wiviott SD, Saucedo JF, Antman EM, Jacobs AK, Wang TY. Use of emergency medical service transport among patients with ST-segment-elevation myocardial infarction: findings from the National Cardiovascular Data Registry Acute Coronary Treatment Intervention Outcomes Network Registry–Get With the Guidelines. *Circulation*. 2011;124:154–163.
- Conrotto F, D'Ascenzo F, Humphries KH, Webb JG, Scacciatella P, Grasso C, D'Amico M, Biondi-Zoccai G, Gaita F, Marra S. A meta-analysis of sex-related differences in outcomes after primary percutaneous intervention for ST-segment elevation myocardial infarction. *J Interv Cardiol*. 2015;28:132–140.
- Rokos IC, French WJ, Koenig WJ, Stratton SJ, Nighswonger B, Strunk B, Jewell J, Mahmud E, Dunford JV, Hokanson J, Smith SW, Baran KW, Swor R, Berman A, Wilson BH, Aluko AO, Gross BW, Rostyus PS, Salvucci A, Dev V, McNally B, Manoukian SV, King SB III. Integration of pre-hospital electrocardiograms and ST-elevation myocardial infarction receiving center (SRC) networks: impact on door-to-balloon times across 10 independent regions. *JACC Cardiovasc Interv*. 2009;2:339–346.

SUPPLEMENTAL MATERIAL

Data S1: List of covariates

Demographics

Age (year)

Sex

Race

Weight (kg)

Medical history

Hypertension

Current/recent smoker

Diabetes mellitus

Dyslipidemia

Prior myocardial infarction

Prior percutaneous coronary intervention

Prior coronary artery bypass graft surgery

Prior heart failure

Prior stroke

Prior peripheral arterial disease

Signs and symptoms at presentation

Heart failure

Cardiogenic shock

Heart rate (bpm)

Systolic blood pressure (mmHg)

Laboratory results

Baseline hemoglobin (g/dL)

Baseline serum creatinine (mg/dL)

Baseline troponin ratio (\times ULN)

Home medications

Aspirin

Clopidogrel

Warfarin

β -Blocker

Angiotensin-converting enzyme inhibitor

Angiotensin receptor blocker

Aldosterone blocking agent

Statin

Non-statin lipid-lowering agent

Other

Insurance status

Mode of transport*

Pre-hospital ECG*

Symptom onset to first medical contact*

*Additional covariates included for this project