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ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Delayed Care and Mortality Among Women and Men With Myocardial Infarction

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***Background*—**Women with ST-segment–elevation myocardial infarction (STEMI) have higher mortality rates than men. We investigated whether sex-related differences in timely access to care among STEMI patients may be a factor associated with excess risk of early mortality in women.

***Methods and Results*—**We identified 6022 STEMI patients who had information on time of symptom onset to time of hospital presentation at 41 hospitals participating in the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) registry (NCT01218776) from October 2010 through April 2016. Patients were stratified into time-delay cohorts. We estimated the 30-day risk of all-cause mortality in each cohort. Despite similar delays in seeking care, the overall time from symptom onset to hospital presentation was longer for women than men (median: 270 minutes [range: 130–776] versus 240 minutes [range: 120–600]). After adjustment for baseline variables, female sex was independently associated with greater risk of 30-day mortality (odds ratio: 1.58; 95% confidence interval, 1.27–1.97). Sex differences in mortality following STEMI were no longer observed for patients having delays from symptom onset to hospital presentation of ≤1 hour (odds ratio: 0.77; 95% confidence interval, 0.29–2.02).

***Conclusions*—**Sex difference in mortality following STEMI persists and appears to be driven by prehospital delays in hospital presentation. Women appear to be more vulnerable to prolonged untreated ischemia.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov/. Unique identifier: NCT01218776. **(*J Am Heart Assoc*. 2017;6: e005968. DOI: 10.1161/JAHA.117.005968.)**

Key Words: acute coronary syndrome • mortality • prehospital delay • women

Controversies abound when examining sex differences in mortality following acute ST-segment–elevation myocardial infarction (STEMI).[1,2] Some studies point to a disadvantage for women in the setting of STEMI.[3,4] Others show similar outcome profiles for women and men.[5] Most of these studies, however, focused only on clinical covariates, which should be viewed cautiously, remembering that therapeutic interventions have a large impact on outcomes.[6] Indeed, when rates of coronary revascularization and delays in revascularization differ between men and women, the value of sex as a prognostic factor may be under- or overestimated by analyses that include patients with such marked differences in treatment. Careful adjustment for differing use of reperfusion therapies and time to treatment is important

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Accompanying Data S1, Tables S1 through S8 and Figure S1 are available at http://jaha.ahajournals.org/content/6/8/e005968/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Our analyses indicate that sex differences in outcomes persist among patients with ST-segment–elevation myocardial infarction and appear to be driven by prehospital delays in hospital presentation; however, higher 30-day mortality of women compared with men after ST-segment–elevation myocardial infarction was confined to times from symptom onset to presentation >1 hour. Consequently, women appear to be more vulnerable to prolonged untreated ischemia.

What Are the Clinical Implications?

- Reducing the time lag between onset of ischemic symptoms and hospital presentation to ≤1 hour is of the utmost importance, especially for women.

because women are less likely to receive timely in-hospital reperfusion therapy.

The timeliness of reperfusion therapy in STEMI depends largely on patients' health awareness, ability to recognize the early signs or symptoms, and access to health services and on hospital quality performance, specifically door-to-balloon and door-to needle times. Several studies have focused on the associations between door-to-balloon and door-to needle delays and outcomes.[7,8] Fewer studies have investigated the associations between overall treatment delay and mortality.[9] No studies have evaluated the effect of treatment delays on sex differences in early cardiac mortality. This study investigated whether sex-based differences in access to care for patients with STEMI were associated with differences in outcomes.

Methods

Setting and Design

ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries; ClinicalTrials.gov identified NCT01218776.) is a large observational registry initiated in 2010. The protocol was described previously.[10–14] Briefly, ISACS-TC is an investigator-driven initiative designed to include information on risk factors, clinical presentation, and complications of acute coronary syndromes. The registry accurately records times to medications and interventions. ISACS-TC mainly includes hospitals in countries with an economy in transition. The aim of ISACS-TC is to provide a large multinational registry of the full spectrum of patients with acute coronary syndromes to develop and evaluate survey measures that elicit improved outcomes in countries embarked on reforming their healthcare systems. Patients were enrolled from 41 geographically diverse sites. Of these hospitals, 22 were tertiary healthcare services providing advanced medical investigation and treatment including percutaneous coronary intervention (PCI) and/or cardiac surgery, and 19 were secondary healthcare services providing intensive care in critical coronary care units (Data S1). The study was approved by the local research ethics committee from each hospital. Because patient information is collected anonymously, institutional review boards waived the need for individual informed consent. The data coordinating center was established at the University of Bologna.

Patients and Procedures

The study population consisted of 8997 eligible patients with STEMI or new, or presumed new, bundle-branch block myocardial infarction enrolled between October 2010 to April 2016. Eligibility was defined by diagnostic changes on the initial 12-lead ECG, presentation, and no contraindications to reperfusion therapy.[15] Patients were defined as having a contraindication to reperfusion therapy if they presented to the enrolling sites within the first 12 hours of symptom onset but were not offered primary PCI or fibrinolysis (Table S1). Patients who had facilitated and rescue PCI or coronary artery bypass grafting were excluded from the analysis. Patients with unknown time of symptom onset were also excluded. Overall, 2975 of 8997 patients were excluded. The fact that 1801 of 8997 patients (20%) were excluded because of unknown time of symptom onset is consistent with findings from previous investigations[16] (Table S2). The final analysis population had 6022 participants (Figure).

Data Collection and Definitions

The enrolled hospitals periodically uploaded their data to the central server of the ISACS-TC. Registry data were collected by the designated physician at the time of clinical assessment. Killip classification at admission was determined by the attending physician in the emergency department.[17] Patients were asked about the quality of their symptoms. Typical chest pain was defined as any symptom of chest discomfort characterized by a sensation or pressure or tightness under the sternum or chest bone, with pain that may radiate to jaw, arms, or neck. The variable of atypical chest pain included both patients with atypical symptoms and those who were asymptomatic. Chest pain was considered to be atypical when its distribution was unusual, such as pressure or pain in the lower chest or upper abdomen or pain or discomfort in one or both arms, the back, or the stomach. Patients with angina "equivalents," such as dyspnea, and fatigue, were defined as asymptomatic.

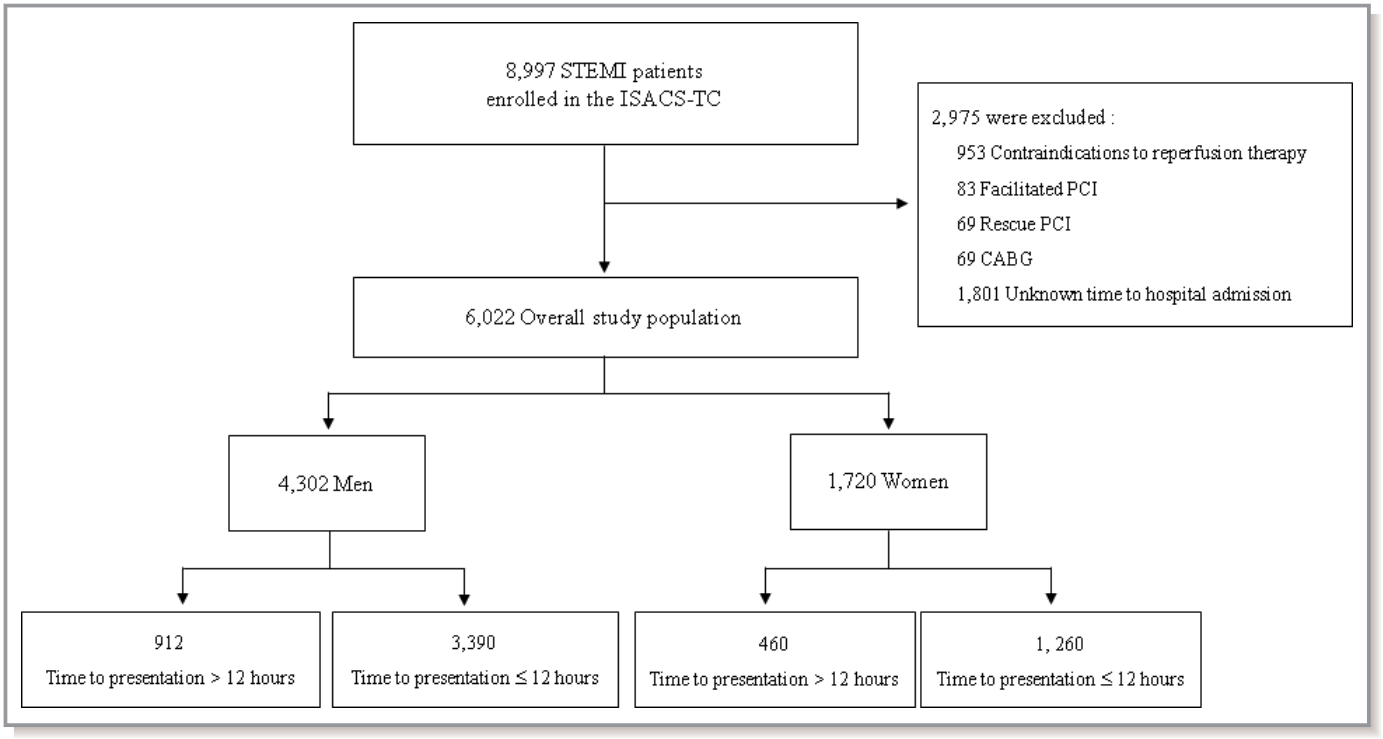


Figure. Flow diagram of patients entered into the study. CABG indicates coronary artery bypass grafting; ISACS-TC, International Survey of Acute Coronary Syndromes in Transitional Countries; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

Treatment Delays

The estimates of various delays in the initiation of reperfusion therapy were based on prehospital data registered by the local hospital provider. Data were then registered in the ISACS-TC registry. Different delays were classified into 5 categories, and each was given an operational definition. Time to presentation (category 1) was the time lag from symptom onset to in-hospital diagnosis. In the ISACS-TC registry, any patient with symptoms suggestive of myocardial infarction should have a 12-lead ECG taken as soon as possible on arrival at the emergency department. Time to first medical contact (category 2) was the time lag from symptom onset to the call seeking care, which included calls to emergency medical services (EMS) or a general physician's office. Calls for EMS were registered at the dispatch center. Data on calls for a general physician's office were based on physician self-reports of scheduled calls and visit times. These estimates were documented when the registry data were collected. Time from first medical contact to hospital presentation (category 3) was the time lag from call for help contacting EMS or a general physician's office to arrival at the emergency department. If patients were admitted to a secondary hospital and then transferred to a tertiary PCI-capable hospital, time from first medical contact to hospital presentation included departure from the secondary hospital and arrival at the PCI center. Self-presenters who reached the hospital just by walking or using public transportation or personally operated vehicles were included in the analysis provided that they had previously contacted their general physician. Door-to needle (category 4) was the time lag from arrival at the local emergency department to the beginning of fibrinolytic therapy. Door-to-balloon (category 5) was the time lag from arrival at the emergency department of the PCI center to first balloon inflation during primary PCI.

End Points and Measurements

The primary outcome was the incidence of 30-day all-cause mortality. The analysis evaluated patient outcomes from hospital admission through the end of the follow-up period. The use of medications given at hospital admission was noted, as well as the use of primary PCI or fibrinolysis. Information on treatment delays was obtained from review of the medical records. The rationale for using limit cutoffs of 12, 4, 2, and 1 hour for time to presentation was based on international guidelines,[18,19] targets set by the UK National Service Framework,[20] and previous data regarding infarct development in men.[21–24] We also studied the likelihood of having cardiogenic shock (Killip class IV) diagnosed at presentation.

Statistical Analysis

Statistical testing of patient characteristics by sex was performed with the use of the χ^2 test for categorical variables

and the Wilcoxon rank sum test for continuous and ordinal variables. Descriptive statistics using medians with 25th and 75th percentiles for continuous variables and percentages for discrete variable were generated for baseline characteristics by these groups. Statistical evaluation was performed using STATA 11 (StataCorp). All *P* values were 2-sided and were considered statistically significant if ≤0.05.

Clinical end point of 30-day all-cause mortality

The clinical end point of 30-day all-cause mortality was compared between the overall population of men and women with STEMI using estimates of the odd ratios (OR) and associated 95% confidence intervals (CIs). Patients were also stratified into time-delay cohorts for time to presentation: ≤1, >1 to ≤2, >2 to ≤4, >4 to ≤12, and >12 hours. Fixed covariates included in the analyses were sex, age, cardiovascular risk factors (history of hypercholesterolemia, history of diabetes mellitus, history of hypertension, family history of coronary artery disease, smoking status), clinical history of ischemic heart disease (prior angina, prior myocardial infarction [MI], prior PCI, and prior coronary artery bypass grafting), clinical history of cardiovascular disorders (prior heart failure and prior stroke), history of chronic kidney disease, and clinical presentation (systolic blood pressure, heart rate, and atypical chest pain). Medications and procedures at hospital admission were included in the analyses as categorical variables. Statistical adjustments were made for primary PCI, fibrinolysis, aspirin, clopidogrel, unfractioned heparin, beta blockers, and angiotensin-converting enzyme inhibitors.

Prehospital delays and cardiogenic shock at hospital admission

The covariate-adjusted association between prehospital delays and cardiogenic shock was assessed by multivariate logistic regression considering all preadmission clinical variables, specifically sex, age, cardiovascular risk factors, clinical history of ischemic heart disease, cardiovascular disorders, and chronic kidney disease.

Missing values and mortality

We had complete data on age, sex, and 30-day mortality. Some patients had missing data on other variables. We multiply imputed the missing values of the variables with a missing rate <10% using STATA software. For the features with a missing rate >10%, we carried out a Pearson χ^2 statistical test for independence between those features and mortality. Only the variables of hypercholesterolemia and atypical chest pain had missing rates >10% and were found to be statistically dependent on the end point mortality. Consequently, we did not dismiss these variables from the predictive model of mortality, and we kept them as missing.[25]

Results

From October 2010 through April 2016, a total of 8997 STEMI patients at 41 sites in 12 countries were enrolled in the ISACS-TC registry. Of these 8997 patients, 6022 were included in the current analysis. Figure shows the flow diagram of patients entered into the study. There were 1372 (22.8%) patients who sought medical attention 12 hours after symptom onset and did not receive any reperfusion therapy (primary PCI or fibrinolysis) Table S3).

Sample Characteristics

Baseline characteristics of the patients are shown in Table 1. The cohort was predominantly male. Women were older and more often had diabetes mellitus and hypertension but were less likely to have a history of prior myocardial infarction or to be smokers. They were given less antithrombotic medication and fibrinolysis (12.8% versus 14.8% Table 1).

Delays to Hospital Presentation

Despite similar delays in seeking care, women were more likely to experience longer prehospital delays than men (Table 2). The median duration of time from symptom onset to in-hospital diagnosis in women was 270 minutes and in men was 240 minutes. Delay in hospital presentation was mainly related to the time lag between first medical contact and hospital presentation. The median differences between women and men ranged from 20 to 45 minutes. Women had 30 more minutes from time of symptom onset to hospital presentation. Of note, no significant differences were observed between women and men in door-to-balloon and door-to-needle times. Table 2 summarizes differences in the distributions of men and women according to the designated time-delay cohorts after symptom onset. The proportion of patients presenting >12 hours after the onset of symptoms was greater among women than men (27.7% versus 21.2%). Patients arriving at the hospital within 2 hours of symptom onset were more likely to be male (30.8% versus 24.2%). Similar findings were observed when using a cut point at 4 hours to separate early from late care seekers (53.4% versus 47.4%). In multivariable analysis adjusted for other predictors of mortality, time from symptom onset to in-hospital diagnosis was independently associated with mortality in patients presenting to the hospital within 48 hours (OR of 1.02 [95% CI, 1.01–1.03] per 1-hour delay; Table S4).

Role of EMS and PCI-Capable Hospitals

A variety of factors may be associated with more prolonged time from first medical contact to hospital presentation in

Table 1. Baseline Characteristics of the Participants

Characteristics	Overall Study Population (N=6022)	Men (n=4302)	Women (n=1720)	*P* Value*
Age (y), mean±SD	60.9±11.7	59.3±11.5	64.8±11.4	<0.001
Cardiovascular risk factors				
Hypercholesterolemia, n/total, %	2041/5262 (38.8)	1458/3771 (38.7)	583/1491 (39.1)	0.76
Diabetes mellitus, n, %	1328 (22.1)	827 (19.2)	501 (29.1)	<0.001
Hypertension, n, %	3738 (62.1)	2509 (58.3)	1229 (71.4)	<0.001
Current smoker, n, %	2530 (42.0)	2003 (46.6)	527 (30.6)	<0.001
Family history of CAD, n, %	1843 (30.6)	1276 (29.7)	567 (32.9)	0.007
Clinical history of ischemic heart disease				
Prior angina pectoris, n, %	713 (11.8)	474 (11.1)	239 (13.9)	0.002
Prior myocardial infarction, n, %	736 (12.2)	558 (12.9)	178 (10.3)	0.005
Prior PCI, n, %	833 (13.8)	599 (13.9)	234 (13.6)	0.75
Prior CABG, n, %	57 (0.9)	44 (1.0)	13 (0.8)	0.33
Clinical history of cardiovascular disorders				
Prior heart failure, n, %	186 (3.1)	125 (2.9)	61 (3.5)	0.19
Prior stroke, n, %	254 (4.2)	161 (3.7)	93 (5.4)	0.004
Clinical presentation				
Atypical chest pain, n/total, %	220/4623 (4.8)	144/3281 (4.4)	76/1342 (5.7)	0.065
Systolic BP at baseline (mm Hg), mean±SD	139.9±24.7	140.1±24.2	139.6±26.3	0.49
Heart rate at baseline (bpm), mean±SD	80.4±22.8	80.2±22.1	81.2±24.3	0.13
Chronic kidney disease, n, %	266 (4.2)	177 (4.1)	89 (5.2)	0.16
In-hospital acute medications				
Aspirin, n, %	5911 (98.2)	4238 (98.5)	1673 (97.3)	0.004
Clopidogrel, n, %	5563 (92.4)	4000 (92.9)	1563 (90.9)	0.01
Unfractioned heparin, n, %	3766 (62.5)	2774 (64.5)	992 (57.7)	<0.001
LMWH, n, %	1687 (28.0)	1214 (28.2)	473 (27.5)	0.24
Fondaparinux, n, %	170 (2.8)	121 (2.8)	49 (2.8)	0.25
Beta blockers, n, %	1317 (21.9)	987 (22.9)	330 (19.2)	0.006
ACEIs, n, %	1426 (23.7)	1068 (24.8)	358 (20.8)	0.004
Reperfusion therapy				
Primary PCI, n, %	4222 (70.1)	3067 (71.3)	1155 (67.1)	0.002
Fibrinolysis, n, %	860 (14.3)	639 (14.8)	221 (12.8)	0.04
Outcomes				
30-Day all-cause mortality, n, %	413 (6.9)	228 (5.3)	185 (10.8)	<0.001

ACEI indicates angiotensin-converting enzyme inhibitor; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LMWH, low-molecular-weight heparins; PCI, percutaneous coronary intervention.
**P* value derived from comparison between men and women.

women. Among these factors, we analyzed sex differences in rates of transportation to hospitals by EMS ambulance and in priority for transport to PCI-capable hospitals. In the overall study population, 42% of patients turned to the EMS as their first medical contact (42.9% of men and 40.3% of women). After adjustment for demographic and clinical factors, women had similar odds of being transported to the hospital by ambulance (OR: 0.91; 95% CI, 0.77–1.06; *P*=0.24). Patients presenting to a non–PCI-capable hospital and requiring transfer to a PCI-capable hospital were mostly men (27.4% versus 24.9%). Similarly, more men than women received fibrinolysis (14.8% versus 12.8%; Table 1). A reason for these

Table 2. Delays and Stages of the Process of Treatment

	Overall Study Population (N=6022)	Men (n=4302)	Women (n=1720)	*P* Value*
Median delays				
Time to from first medical contact (min), median (IQR)	50 (20–180)	50 (20–180)	60 (15–180)	0.60
Time from first medical contact to hospital presentation (min), median (IQR)	67 (40–130)	60 (40–120)	88 (60–165)	0.001
Time to presentation (min), median (IQR)	240 (120–650)	240 (120–600)	270 (130–776.5)	<0.001
Door to needle (min), median (IQR)	27 (15–42)	26 (15–41)	28 (15–43.5)	0.56
Door to balloon (min), median (IQR0	45 (25–80)	45 (27–80)	45 825–75)	0.11
Time-delay cohorts				
Time to presentation >12 h, n, %	1372 (22.8)	912 (21.2)	460 (27.7)	<0.001
Time to presentation >4 to ≤12 h, n, %	1536 (25.5)	1091 (25.4)	445 (25.9)	<0.001
Time to presentation >2 to ≤4 h, n, %	1372 (22.8)	973 (22.6)	399 (23.2)	<0.001
Time to presentation >1 to ≤2 h, n, %	1022 (16.9)	779 (18.1)	243 (14.1)	<0.001
Time to presentation ≤1 h, n, %	720 (11.9)	547 (12.7)	173 (10.1)	<0.001

IQR indicates interquartile range.
**P* value derived from comparison between men and women.

findings may be that women presented later and often out of the fibrinolytic window of 12 hours (21.7% versus 13.8%). Among patients who required transfer from a non–PCI-capable to a PCI-capable hospital, women had a median time from symptom onset to PCI at the final hospital destination of 400 minutes compared with 360 minutes for men (Table S5). In the model considering only the group of patients transferred by EMS ambulance directly to a PCI-capable hospital, women still had a median time to presentation of 210 minutes compared with 180 minutes for men.

Impact of Various Treatment Delays

When all of the baseline clinical variables (fixed covariates) were assessed simultaneously in multivariable analysis (Table 3), 6 remained significant predictors of 30-day all cause mortality: older age, female sex, prior stroke, chronic kidney disease, and clinical presentation with higher heart rate or lower systolic blood pressure. The adjusted OR for mortality associated with female sex did not change when controlling for medication use at admission (Table S6). Estimates of mortality in women compared with men were repeated in the time-delay cohorts for time to hospital presentation (≤1, >1 to ≤2, >2 to ≤4, >4 to ≤12, >12 hours; Table 4). Significant sex difference was no longer observed for patients having delays in time to presentation of <2 hours. Of note, similar odds for 30-day mortality were observed with delays of ≤1 hour (OR: 0.77; 95% CI, 0.29–2.02). After adjusting for demographic and clinical covariates, the ORs for 30-day mortality in women were 0.29 (95% CI, 0.13–0.64) for time to presentation ≤1 hour; 0.53 (95% CI, 0.30–0.95) for >1 to ≤2 hours; 0.61 (95% CI, 0.38–0.97) for >2 to ≤4 hours; and 0.61 (95% CI, 0.40–0.95) for >4 to ≤12 hours. The corresponding values in the overall population were 0.46 (95% CI, 0.30–0.71), 0.55 (95% CI, 0.39–0.78), 0.59 (95% CI, 0.44–0.81), and 0.54 (95% CI, 0.40–0.72), respectively. We conducted further analyses to assess the robustness of our results. First, we used the variable of time to presentation as a covariate rather than to stratify the data by delay cohorts (Figure S1). A strong and graded relation was noted between time to presentation and risk of 30-day mortality, with the risk decreasing at every time decrement of the delay, so that patients with a time to presentation ≤1 hour had an OR of 0.30 (95% CI, 0.20–0.44) compared with the reference group of patients with a time to presentation >12 hours. This relationship was stronger for women. We then performed an interaction test between time to presentation ≤1 hour (reference group) and delay of ≥12 hours. Results were similar, although risk differences were attenuated (Table S7). The OR for women compared with men having 30-day mortality was 1.43 (95% CI, 1.03–1.98) with no significant interaction effect.

Cardiogenic Shock

Information on Killip classification at admission was available for 4003 patients. Women had higher unadjusted and adjusted risk of having a diagnosis of cardiogenic shock (Killip class IV) at hospital admission than men (Table S8). Comparison of time-delay cohorts revealed that the risk of

Table 3. Multivariate Analysis of Factors Associated With 30-Day All-Cause Mortality

	OR	95% CI	*P* Value
Unadjusted	2.15	1.76–2.64	<0.001
Multivariate adjusted			
Women	1.58	1.27–1.97	<0.001
Age	1.07	1.05–1.08	<0.001
Hypercholesterolemia	0.99	0.96–1.04	0.95
Diabetes mellitus	1.05	0.99–1.12	0.10
Hypertension	1.01	0.92–1.11	0.80
Current smoker	1.03	0.95–1.11	0.51
Family history of CAD	1.04	0.99–1.08	0.070
Atypical chest pain	1.01	0.98–1.04	0.56
Heart rate at admission (per 1-SD increment*)	1.38	1.22–1.55	<0.001
Systolic blood pressure at admission (per 1-SD increment*)	0.57	0.52–0.63	<0.001
Prior angina pectoris	0.79	0.56–1.11	0.18
Prior myocardial infarction	1.02	0.73–1.44	0.87
Prior PCI/CABG	1.26	0.91–1.73	0.15
Prior heart failure	1.22	0.74–1.97	0.42
Prior stroke	1.99	1.37–2.91	<0.001
Chronic kidney disease	1.36	1.20–1.54	<0.001

*SDs for heart rate and systolic blood pressure are 23 bpm and 25 mm Hg.

cardiogenic shock was significantly greater for women compared with men of similar age and similar risk profile when time to hospital presentation was >4 hours (adjusted OR: 1.80; 95% CI, 1.04–3.14).

Discussion

The main finding of the current study is that sex differences in 30-day all-cause mortality following STEMI persist and appear to be driven by delays in presentation to the hospital. In general, women were more likely to experience longer delays than men. Increasing time to presentation was associated with an increasing rate of mortality in both sexes. Notably, simple time-delay adjustment eliminated the sex difference in mortality rate for patients with delays from symptom onset to hospital presentation of ≤1 hour. The present study, therefore, not only indicates that women have greater prehospital delays to presentation after STEMI, and consequently greater mortality, but also demonstrates a differential effect of sex on the association between delays and mortality. These findings raise concerns about treatment and triage strategies used by first responders and about transfer procedures between hospitals. These data also suggest that women are more vulnerable than men to prolonged untreated ischemia.

Previous Studies

Consistent with many studies conducted in diverse clinical settings, this study found that women with STEMI are at greater risk of 30-day all-cause mortality compared with men, despite adjustment for clinical baseline variables.[6,26–28] Our analysis, however, differs from previous reports of outcomes following STEMI because prior studies have not looked at sex differences in outcomes adjusted for time from symptom onset to hospital presentation and subsequent late or no utilization of cardiac revascularization procedures, and rates of revascularization are typically and significantly lower in women compared with men.[4,29–33]

Sources of Delays

Several studies have documented that delays can occur from different sources, including patients and providers and the healthcare system itself.[34,35] We demonstrated that women with suspicion of STEMI have longer times for calling medical services, longer times to hospital presentation, and ultimately significantly delayed use of reperfusion therapies. Previous work has shown that women have longer door-to-balloon times[36] and longer door-to-needle times.[37] This was not observed in the current study, which showed similar in-hospital times for reperfusion therapy once STEMI was documented at the emergency department.

Patient-Related Delays

Our data demonstrate that women are more likely than men to encounter delays between the onset of symptoms and first medical contact.[3,38,39] We do not have data about whether the problem from the perspective of the women is related to symptom recognition, symptom interpretation, or decisions related to care seeking, including the mode of transportation to the hospital. Women with chest pain often may consider their symptoms normal and seek help from incorrect sources.[3,38,39] Angina in women can manifest as atypical chest pain or dyspnea.[3,38] In our study, the proportion of patients with atypical presentation of chest pain was higher for women than for men, but this finding was uncommon for both sexes (6% versus 4%), and thus cannot entirely explain the large difference in the delay in hospital presentation between women and men.[40]

Delays on the Part of the Healthcare System

Our study found longer delays on the part of the health system than on the part of patients. Only a minority of patients

Table 4. Impact of Various Treatment Delays on the Odds of Mortality for Women

	OR (95% CI)	*P* Value	Unadjusted Event rate, %
Model 1: Overall study population adjusted for demographic and clinical factors			
30-Day all-cause mortality in all STEMI population	1.58 (1.27–1.97)	<0.001	6.9
30-Day all-cause mortality in patients receiving pPCI	1.56 (1.25–1.95)	<0.001	4.8
30-Day all-cause mortality in patients receiving fibrinolysis	1.58 (1.27–1.97)	<0.001	7.8
Model 2: Time to presentation >12 h (n=1372)			
30-Day all-cause mortality in all STEMI population	1.57 (1.09–2.25)	0.015	12.4
Model 3: Time to presentation >4 to ≤12 h (n=1536)			
30-Day all-cause mortality in all STEMI population	1.73 (1.09–2.76)	0.020	5.7
30-Day all-cause mortality in patients receiving pPCI	1.71 (1.07–2.73)	0.023	5.1
30-Day all-cause mortality in patients receiving fibrinolysis	1.71 (1.07–2.74)	0.023	9.5
Model 4: Time to presentation >2 to ≤4 h (n=1372)			
30-Day all-cause mortality in all STEMI population	1.77 (1.05–2.99)	0.031	5.5
30-Day all-cause mortality in patients receiving pPCI	1.84 (1.08–3.11)	0.023	4.8
30-Day all-cause mortality in patients receiving fibrinolysis	1.84 (1.09–3.11)	0.023	8.7
Model 5: Time to presentation >1 to ≤2 h (n=1022)			
30-Day all-cause mortality in all STEMI population	1.29 (0.65–2.58)	0.46	4.9
30-Day all-cause mortality in patients receiving pPCI	1.29 (0.65–2.59)	0.46	4.5
30-Day all-cause mortality in patients receiving fibrinolysis	1.29 (0.65–2.59)	0.46	6.4
Model 6: Time to presentation ≤1 h (n=720)			
30-Day all-cause mortality in all STEMI population	0.77 (0.29–2.02)	0.59	4.0
30-Day all-cause mortality in patients receiving pPCI	0.75 (0.28–1.99)	0.57	3.8
30-Day all cause mortality in patients receiving fibrinolysis	0.75 (0.28–1.99)	0.57	4.9

CI indicates confidence interval; OR, odds ratio; pPCI indicates primary percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

(28.8%) reached the hospital within 2 hours. Delays in presentation to the hospital (48.3%) mostly ranged between 2 and 12 hours. Women were more likely to experience longer delays to hospital presentation than men, in keeping with previous work.[41,42] The different twist in this study was that delay to hospital presentation was mainly related to the time lag between first medical contact and hospital presentation, which stimulates concern about the system-related causes. Provider delays primarily involve lack of early diagnosis and/or lower priority for ambulance transport to a PCI-capable hospital. Our data indicate no significant difference among the rates of women and men using EMS. Similar data on the use of EMS have been reported in the United States and Sweden.[43,44] Contrary to expectations, women showed significantly higher rates of admission to primary PCI-capable hospitals; however, prehospital delays were still greater among women. These findings underscore the need to improve the management of female patients, even at the EMS centers, perhaps by improving the use of prehospital 12-lead ECG for early identification of STEMI.[45] There is a need for transfer algorithms, including EMS, non-PCI hospitals/STEMI referring centers, and PCI hospitals/STEMI receiving centers, to evaluate outcomes and quality improvement data.[46]

Delays to Hospital Presentation and Sex Differences in Mortality

Overall, 30-day mortality was higher for women compared with their male counterparts in the study population. Although 5.3% of men died within 30 days, the mortality rate for women was nearly double at 10.8%. Increasing delay in presentation was associated with an adjusted increase in 30-day mortality for all time cohorts in both women and men; however, when the sample was subdivided into time cohorts, no sex difference in mortality was found in the lowest time-delay group (<1 hour, OR: 0.77; 95% CI, 0.29–2.02), whereas among patients arriving later, women showed a higher mortality rate compared with men, ranging from adjusted ORs of 1.29 to 1.73.

Sex Differences in Response to Prolonged Untreated Ischemia

The mechanism of why a delay of >1 hour is associated with poorer survival in women compared with men could not be completely ascertained. Women were significantly more likely to experience cardiogenic shock in all groups of delay >4 hours, suggesting that some biological differences between sexes may contribute to altered myocardial response to infarction, which also may constitute a possible mechanism to explain different rates of mortality.[47–49]

Study Limitations

Some limitations in the current analyses must be noted. First, our data are observational, and thus some degree of residual confounding cannot be excluded; however, the effects of different prehospital delays on mortality cannot be subjected to randomized assessments. Second, we were unable to determine whether prehospital characteristics of the patient's home and rural location could have played a role in the delays in hospital presentation and treatment. Although such information might have provided useful insights, its absence does not compromise the actual findings of the study. Third, the geographical and organizational conditions of the ISACS-TC registry may not necessarily apply to other countries and regions.

Conclusions

Our analyses indicate that sex differences in outcomes persist among STEMI patients and appear to be driven by prehospital delays in hospital presentation. Higher 30-day mortality among women compared with men after STEMI is confined to times from symptom onset to presentation >1 hour. Reducing the time lag between onset of ischemic symptoms and hospital presentation is of the utmost importance for women because they seem to be more vulnerable to prolonged untreated ischemia. Further investigations may address the mechanisms that make women more vulnerable.

Disclosures

None.

References

1. Vaccarino V, Badimon L, Corti R, de Wit C, Dorobantu M, Manfrini O, Koller A, Pries A, Cenko E, Bugiardini R. Presentation, management, and outcomes of ischaemic heart disease in women. *Nat Rev Cardiol*. 2013;10:508–518.
2. Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex differences in long-term mortality after myocardial infarction: a systematic review. *Circulation*. 2014;130:757–767.
3. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133:916–947.
4. Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, Simes RJ, White HD, Van de Werf F, Topol EJ, Hochman JS, Newby LK, Harrington RA, Califf RM, Becker RC, Douglas PS. Sex differences in mortality following acute coronary syndromes. *JAMA*. 2009;302:874–882.
5. Gottlieb S, Harpaz D, Shotan A, Boyko V, Leor J, Cohen M, Mandelzweig L, Mazouz B, Stern S, Behar S. Sex differences in management and outcome after acute myocardial infarction in the 1990s: a prospective observational community-based study. Israeli Thrombolytic Survey Group. *Circulation*. 2000;102:2484–2490.
6. Bugiardini R, Yan AT, Yan RT, Fitchett D, Langer A, Manfrini O, Goodman SG; Canadian Acute Coronary Syndrome Registry I and II Investigators. Factors influencing underutilization of evidence-based therapies in women. *Eur Heart J*. 2011;32:1337–1344.
7. Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, Gore JM, Weaver WD, Rogers WJ, Tiefenbrunn AJ. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000;283:2941–2947.
8. McNamara RL, Herrin J, Wang Y, Curtis JP, Bradley EH, Magid DJ, Rathore SS, Nallamothu BK, Peterson ED, Blaney ME, Frederick P, Krumholz HM. Impact of delay in door-to-needle time on mortality in patients with ST-segment elevation myocardial infarction. *Am J Cardiol*. 2007;100:1227–1232.
9. Terkelsen CJ, Sørensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, Vach W, Johnsen SP, Thuesen L, Lassen JF. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA*. 2010;304:763–771.
10. Bugiardini R, Badimon L, Manfrini O; on the behalf of the ISACS-TC Investigators. Rationale and design of the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) project. *Eur Heart J Suppl*. 2014;16(suppl A): A1–A6.
11. Bugiardini R, Badimon L; ISACS-TC; Investigators and Coordinators. The International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC): 2010–2015. *Int J Cardiol*. 2016;217:S1–S6.
12. Bugiardini R, Cenko E, Ricci B, Vasiljevic Z, Dorobantu M, Kedev S, Vavlukis M, Kalpak O, Puddu PE, Gustiene O, Trninic D, Knežević B, Miličić D, Gale CP, Manfrini O, Koller A, Badimon L. Comparison of early versus delayed oral β blockers in acute coronary syndromes and effect on outcomes. *Am J Cardiol*. 2016;117:760–767.
13. Cenko E, Ricci R, Kedev S, Vasiljevic Z, Dorobantu M, Gustiene O, Knežević B, Miličić D, Dilic M, Trninic D, Smith F, Manfrini O, Badimon L, Bugiardini R. Reperfusion therapy for ST-elevation acute myocardial infarction in Eastern Europe: the ISACS-TC registry. *Eur Heart J Qual Care Clin Outcomes*. 2016;2:45–51.
14. Bugiardini R, Dorobantu M, Vasiljevic Z, Kedev S, Knežević B, Miličić D, Calmac L, Trninic D, Daullxhiu I, Cenko E, Ricci B, Puddu PE, Manfrini O, Koller A, Badimon L; ISACS-TC Investigators. Unfractionated heparin-clopidogrel combination in ST-elevation myocardial infarction not receiving reperfusion therapy. *Atherosclerosis*. 2015;241:151–156.
15. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.
16. Saczynski JS, Yarzebski J, Lessard D, Spencer FA, Gurwitz JH, Gore JM, Goldberg RJ. Trends in prehospital delay in patients with acute myocardial infarction (from the Worcester Heart Attack Study). *Am J Cardiol*. 2008;102:1589–1594.
17. El-Menyar A, Zubaid M, AlMahmeed W, Sulaiman K, AlNabti A, Singh R, Al Suwaidi J. Killip classification in patients with acute coronary syndrome: insight from a multicenter registry. *Am J Emerg Med*. 2012;30:97–103.
18. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Ting HH, O'Gara PT, Kushner FG, Ascheim DD, Brindis RG, Casey DE Jr, Chung MK, de Lemos JA, Diercks DB, Fang JC, 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. 2015 ACC/AHA/SCAI Focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2016;133:1135–1147.

19. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569–2619.
20. Department of Health. The National Service Framework for coronary heart disease: Winning the war on heart disease. Crown copyright; 2004.
21. McGinn AP, Rosamond WD, Goff DC Jr, Taylor HA, Miles JS, Chambless L. Trends in prehospital delay time and use of emergency medical services for acute myocardial infarction: experience in 4 US communities from 1987–2000. *Am Heart J*. 2005;150:392–400.
22. Ting HH, Chen AY, Roe MT, Chan PS, Spertus JA, Nallamothu BK, Sullivan MD, DeLong ER, Bradley EH, Krumholz HM, Peterson ED. Delay from symptom onset to hospital presentation for patients with non-ST-segment elevation myocardial infarction. *Arch Intern Med*. 2010;170:1834–1841.
23. Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, Cutlip DE, Bates ER, Frederick PD, Miller DP, Carrozza JP Jr, Antman EM, Cannon CP, Gibson CM. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. *Circulation*. 2006;114:2019–2025.
24. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol*. 2003;92:824–826.
25. Bennett DA. How can I deal with missing data in my study? *Aust N Z J Public Health*. 2001;25:464–469.
26. Vaccarino V, Badimon L, Corti R, de Wit C, Dorobantu M, Hall A, Koller A, Marzilli M, Pries A, Bugiardini R; Working Group on Coronary Pathophysiology and Microcirculation. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology. *Cardiovasc Res* 2011;90:9–17.
27. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol*. 2009;54:1561–1575.
28. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. *JAMA Intern Med*. 2014;174:1822–1830.
29. De Luca L, Marini M, Gonzini L, Boccanelli A, Casella G, Chiarella F, De Servi S, Di Chiara A, Di Pasquale G, Olivari Z, Caretta G, Lenatti L, Gulizia MM, Savonitto S. Contemporary trends and age-specific sex differences in management and outcome for patients with ST-segment elevation myocardial infarction. *J Am Heart Assoc*. 2016;5:e004202. DOI: 10.1161/JAHA.116.004202.
30. Khera S, Kolte D, Gupta T, Subramanian KS, Khanna N, Aronow WS, Ahn C, Timmermans RJ, Cooper HA, Fonarow GC, Frishman WH, Panza JA, Bhatt DL. Temporal trends and sex differences in revascularization and outcomes of ST-segment elevation myocardial infarction in younger adults in the United States. *J Am Coll Cardiol*. 2015;66:1961–1972.
31. de Boer SP, Roos-Hesselink JW, van Leeuwen MA, Lenzen MJ, van Geuns RJ, Regar E, van Mieghem NM, van Domburg R, Zijlstra F, Serruys PW, Boersma E. Excess mortality in women compared to men after PCI in STEMI: an analysis of 11 931 patients during 2000–2009. *Int J Cardiol*. 2014;176:456–463.
32. Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, Canto JG, Lichtman JH, Vaccarino V; NRMI Investigators. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. *Heart*. 2009;95:895–899.
33. Gharacholou SM, Alexander KP, Chen AY, Wang TY, Melloni C, Gibler WB, Pollack CV Jr, Ohman EM, Peterson ED, Roe MT. Implications and reasons for the lack of use of reperfusion therapy in patients with ST-segment elevation myocardial infarction: findings from the CRUSADE initiative. *Am Heart J*. 2010;159:757–763.
34. Miedema MD, Newell MC, Duval S, Garberich RF, Handran CB, Larson DM, Mulder S, Wang YL, Lips DL, Henry TD. Causes of delay and associated mortality in patients transferred with ST-segment-elevation myocardial infarction. *Circulation*. 2011;124:1636–1644.
35. Perkins-Porras L, Whitehead DL, Strike PC, Steptoe A. Pre-hospital delay in patients with acute coronary syndrome: factors associated with patient decision time and home-to-hospital delay. *Eur J Cardiovasc Nurs*. 2009;8:26–33.
36. Brodie BR, Hansen C, Stuckey TD, Richter S, Versteeg DS, Gupta N, Downey WE, Pulsipher M. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. *J Am Coll Cardiol*. 2006;47:289–295.
37. D'Onofrio G, Safdar B, Lichtman JH, Strait KM, Dreyer RP, Geda M, Spertus JA, Krumholz HM. Sex differences in reperfusion in young patients with ST-segment-elevation myocardial infarction: results from the VIRGO study. *Circulation*. 2015;131:1324–1332.
38. McSweeney JC, Rosenfeld AG, Abel WM, Braun LT, Burke LE, Daugherty SL, Fletcher GF, Gulati M, Mehta LS, Pettey C, Reckelhoff JF; American Heart Association Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Hypertension, Council on Lifestyle and Cardiometabolic Health, and Council on Quality of Care and Outcomes Research. Preventing and experiencing ischemic heart disease as a woman: state of the science: a scientific statement from the American Heart Association. *Circulation*. 2016;133:1302–1331.
39. Melberg T, Kindervaag B, Rosland J. Gender-specific ambulance priority and delays to primary percutaneous coronary intervention: a consequence of the patients' presentation or the management at the emergency medical communications center? *Am Heart J*. 2013;166:839–845.
40. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G, Zheng ZJ; NRMI Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307:813–822.
41. Moser DK, Kimble LP, Alberts MJ, Alonzo A, Croft JB, Dracup K, Evenson KR, Go AS, Hand MM, Kothari RU, Mensah GA, Morris DL, Pancioli AM, Riegel B, Zerwic JJ. Reducing delay in seeking treatment by patients with acute coronary syndrome and stroke: a scientific statement from the American Heart Association Council on cardiovascular nursing and stroke council. *Circulation*. 2006;114:168–182.
42. Nguyen HL, Saczynski JS, Gore JM, Goldberg RJ. Age and sex differences in duration of prehospital delay in patients with acute myocardial infarction: a systematic review. *Circ Cardiovasc Qual Outcomes*. 2010;3:82–92.
43. Luepker RV. Delay in acute myocardial infarction: why don't they come to the hospital more quickly and what can we do to reduce delay? *Am Heart J*. 2005;150:368–370.
44. Thylén I, Ericsson M, Hellström Ängerud K, Isaksson RM, Sederholm Lawesson S; SymTime study group. First medical contact in patients with STEMI and its impact on time to diagnosis; an explorative cross-sectional study. *BMJ Open* 2015;5:e007059.
45. Daudelin DH, Sayah AJ, Kwong M, Restuccia MC, Porcaro WA, Ruthazer R, Goetz JD, Lane WM, Beshansky JR, Selker HP. Improving use of prehospital 12-lead ECG for early identification and treatment of acute coronary syndrome and ST-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2010;3:316–323.
46. American Heart Association. Recommendations for Criteria for STEMI Systems of Care. Available at: http://www.heart.org/HEARTORG/Professional/MissionLifelineHomePage/EMS/Recommendations-for-Criteria-for-STEMI-Systems-of-Care_UCM_312070_Article.jsp?appName=MobileApp. Accessed April 15, 2017.
47. Kitzman DW. Heart failure with normal systolic function. *Clin Geriatr Med*. 2000;16:489–512.
48. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, LeJemtel TH, Cotter G; SHOCK Investigators. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol*. 2004;44:340–348.
49. Barbash IM, Behar S, Battler A, Hasdai D, Boyko V, Gottlieb S, Leor J. Management and outcome of cardiogenic shock complicating acute myocardial infarction in hospitals with and without on-site catheterisation facilities. *Heart*. 2001;86:145–149.

Supplemental Material

Data S1.

ISACS-TC sites:

Bosnia and Herzegovina: Clinical Center of Banja Luka, Republika Srpska, Banja Luka; Clinical Center University of Sarajevo, Sarajevo; Opšta Bolnica:"Sveti Vracevi"; Opšta Bolnica, Gradiška; Klinički Centar, Kasindo; Dom Zdravlja “Dr Mladen Stojanovć”, Bačka Palanka; Opšta Bolnica “Sveti Apostol Luka”, Doboj; Univesity Clinical Hospital Mostar. **Croatia:** University Hospital Centre of Zagreb, Zagreb; Clinical Hospital Merkur, Zagreb; Clinical Hospital Dubrava, Zagreb. **Italy**: Sapienza-Cuore Grossi Vasi, Rome. **Kosovo:** Clinical Center of Kosovo, Prishtina. **Lithuania:** Hospital of Lithuanian University of Health Sciences, Kaunas. **Macedonia:** University Clinic of Cardiology, Skopje. **Hungary:** University of Pecs, Medical School, 1st Department of Medicine, Division of Cardiology. **Moldova:** Hospital Center of Cardiology; Institute of Cardiology, Chișinău. **Montenegro:** Clinical Center of Montenegro, Podgorica; General Hospital Kotor; Opšta Bolnica Meljine, Herceg Novi; JZU Dom Zdravlja Plav - Interno Odjeljenje; General Hospital Pljevlja; Opšta Bolnica Berane; Opšta Bolnica Bijelo Polje; Opšta Bolnica Danilo I, Cetinje; PZU OB.MELJINE. **Romania:** Spitalul Clinic de Urgenta, Bucaresti; Spitalul Judetean, Baia Mare. **Russian Federation:** Institute of Therapy and Preventive Medicine in Novosibirsk, Russian Academy of Medical Sciences in Novosibirsk. **Serbia:** University of Belgrade, Clinical Center of Serbia, Belgrade; Clinical Hospital Center, Zemun; Zvezdara University Hospital Center; University Hospital Medical Center Bezanijska Kosa; Hospital of Valjevo; City Hospital, Mitrovica; Clinical Center Kragujevac; General Hospital Cuprija; General Hospital Dr. Djordje Joanovic; Cardiology Clinic, Institute for Treatment and Rehabilitation; General Hospital Jagodina; KBC Kosovska Mitrovica.

Table S1. Baseline characteristics of patients with contraindications to reperfusion therapy

Characteristics	Overall population N=953	Men (*N*=590)	Women (*N*=363)	*P*-value†
Age (years), mean±SD	65.8 ± 13.2	62.8 ± 13.4	70.6 ± 11.3	<0.001
Cardiovascular risk factors				
Hypercholesterolemia, *n/total (%)*	261/763 (34.2)	159/475 (33.5)	102/288 (35.4)	0.58
Diabetes, *n (%)*	261 (27.4)	147 (24.9)	114 (31.4)	0.09
Hypertension, *n (%)*	612 (64.2)	349 (59.1)	263 (72.4)	<0.001
Current smoker, *n (%)*	252 (26.4)	190 (32.2)	62 (17.1)	<0.001
Family history of CAD, *n (%)*	235 (24.7)	141 (23.9)	94 (25.9)	0.51
Clinical history of ischemic heart disease				
Prior angina pectoris, *n (%)*	144 (15.1)	87 (14.7)	57 (15.7)	0.69
Prior myocardial infarction, *n (%)*	172 (18.0)	119 (20.2)	53 (14.6)	0.03
Prior PCI, *n (%)*	96 (10.1)	65 (11.0)	31 (8.50)	0.21
Prior CABG, *n (%)*	30 (3.1)	23 (3.9)	7 (1.9)	0.09
Clinical history of cardiovascular disorders				
Prior heart failure, *n (%)*	56 (5.9)	33 (5.6)	23 (6.3)	0.63
Prior stroke, *n (%)*	77 (8.1)	45 (7.6)	32 (8.8)	0.51

Clinical presentation				
Atypical chest pain, n*/total (%)*	106/865 (12.2)	54/536 (10.1)	52/329 (15.8)	0.013
Systolic BP at baseline (mmHg), mean±SD	136.3 ±29.4	135.8 ± 29.7	136.9 ± 28.8	0.55
Heart rate at baseline (b.p.m.), mean±SD	83.3 ± 22.9	83.2 ± 23.4	83.5 ± 22.2	0.83
Chronic kidney disease, *n (%)*	103 (10.8)	60 (10.2)	463 (0.8)	0.59
In-hospital acute medications				
Aspirin, *n (%)*	849 (89.1)	535 (90.7)	314 (86.5)	0.11
Clopidogrel, *n (%)*	652 (68.4)	415 (70.3)	237 (65.3)	0.11
Unfractioned heparin, *n (%)*	381 (39.4)	241 (40.8)	140 (38.6)	0.37
LMWH, *n (%)*	405 (42.5)	252 (42.7)	153 (42.1)	0.33
Fondaparinux, *n (%)*	29 (3.1)	19 (3.2)	10 (2.7)	0.36
B-blockers, *n (%)*	171 (17.9)	108 (18.3)	63 (17.4)	0.51
ACE-inhibitors, *n (%)*	168 (17.6)	111 (18.8)	57 (15.7)	0.33
Outcomes				
30-day all-cause mortality, *n (%)*	162 (17.0)	88 (14.9)	74 (20.4)	0.03

†*P*-value derived from comparison between men and women. BP, blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LMWH, Low molecular weight heparins; ACE, angiotensin-converting-enzyme.

Table S2. Baseline characteristics of patients with unknown time of symptom onset

Characteristics	Overall population N=1801	Men (*N*=1231)	Women (*N*=570)	*P*-value†
Age (years), mean±SD	62.5 ± 12.2	60.3 ± 11.5	67.4 ± 12.2	<0.001
Cardiovascular risk factors				
Hypercholesterolemia, *n/total (%)*	642/1431 (44.9)	429/972 (44.1)	213 /459 (46.4)	0.42
Diabetes, *n (%)*	457 (25.4)	290 (23.6)	167 (29.3)	0.02
Hypertension, *n (%)*	1177 (65.3)	753 (61.2)	424 (74.4)	<0.001
Current smoker, *n (%)*	728 (40.4)	563 (45.7)	165 (29.9)	<0.001
Family history of CAD, *n (%)*	576 (31.9)	397 (32.2)	179 (31.4)	0.89
Clinical history of ischemic heart disease				
Prior angina pectoris, *n (%)*	417 (23.1)	261 (21.2)	156 (27.4)	0.004
Prior myocardial infarction, *n (%)*	186 (10.33)	131 (10.6)	550 (9.6)	0.52
Prior PCI, *n (%)*	101 (5.6)	74 (6.0)	27 (4.7)	0.27
Prior CABG, *n (%)*	28 (1.55)	23 (1.9)	5 (0.9)	0.11
Clinical history of cardiovascular disorders				
Prior heart failure, *n (%)*	111 (6.2)	71 (5.8)	40 (7.0)	0.30
Prior stroke, *n (%)*	50 (2.8)	31 (2.5)	19 (3.3)	0.32

Clinical presentation				
Atypical chest pain, n/*total (%)*	93/1691 (5.5)	62 (5.4)	31 (5.7)	0.75
Systolic BP at baseline (mmHg), mean±SD	136.6 ± 22.0	137.2 ± 20.3	135.5 ± 25.3	0.12
Heart rate at baseline (b.p.m.), mean±SD	80.5 ± 19.2	80.5 ± 20.0	80.4 ± 17.4	0.87
Chronic kidney disease, *n (%)*	98 (5.44)	54 (4.4)	44 (7.7)	0.003
In-hospital acute medications				
Aspirin, *n (%)*	1695 (94.1)	1164 (94.6)	531 (93.2)	0.42
Clopidogrel, *n (%)*	1610 (89.4)	1099 (89.3)	511 (89.6)	0.95
Unfractioned heparin, *n (%)*	658 (36.5)	442 (35.9)	216 (37.9)	0.70
LMWH, *n (%)*	1,037 (57.6)	710 (57.7)	327 (57.4)	0.95
Fondaparinux, *n (%)*	50 (2.8)	34 (2.8)	16 (2.8)	0.96
B-blockers, *n (%)*	968 (53.7)	681 (55.3)	287 (50.3)	0.14
ACE-inhibitors, *n (%)*	973 (54.0)	674 (54.7)	299 (52.5)	0.63
Reperfusion therapy				
Primary PCI, *n (%)*	1243 (69.0)	878 (71.3)	365 (64.0)	0.001
Fibrinolysis, *n (%)*	207 (11.5)	143 (11.6)	64 (11.2)	0.79
Outcomes				
30-day all-cause mortality, *n (%)*	97 (5.4)	47 (3.8)	50 (8.8)	<0.001

†*P*-value derived from comparison between men and women. BP, blood pressure; CAD,

coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LMWH, Low molecular weight heparins; ACE, angiotensin-converting-enzyme.

Table S3. Baseline characteristics of patients presenting within and after 12 hours from symptom onset

Characteristics	Patients within 12 hours (N=4650)	Patients after 12 hours (N=1372)	P-value
Age (years), mean±SD	60.0 ± 11.4	63.9 ± 12.3	<0.001
Women	1260 (27.1)	460 (33.5)	<0.001
Cardiovascular risk factors			
Hypercholesterolemia, *n/total (%)*	1649/4110 (40.1)	392/1152 (34.0)	<0.001
Diabetes, *n (%)*	959 (20.6)	369 (26.9)	<0.001
Hypertension, *n (%)*	2879 (61.9)	859 (62.6)	0.42
Current smoker, *n (%)*	2118 (45.5)	412 (30.0)	<0.001
Family history of CAD, *n (%)*	1345 (28.9)	498 (36.6)	<0.001
Clinical history of ischemic heart disease			
Prior angina pectoris, *n (%)*	519 (11.1)	194 (14.1)	0.003
Prior myocardial infarction, *n (%)*	546 (11.7)	190 (13.8)	0.036
Prior PCI, *n (%)*	640 (13.8)	193 (14.1)	0.77
Prior CABG, *n (%)*	37 (0.8)	20 (1.5)	0.026
Clinical history of cardiovascular disorders			

Prior heart failure, *n (%)*	121 (2.6)	65 (4.7)	<0.001
Prior stroke, *n (%)*	172 (3.7)	82 (5.9)	<0.001
Clinical presentation			
Atypical chest pain, n/*total (%)*	90/3390 (2.6)	130/1233 (10.5)	<0.001
Systolic BP at baseline (mmHg), mean±SD	140.9 ± 24.6	136.5 ± 26.9	<0.001
Heart rate at baseline (b.p.m.), mean±SD	80.0 ± 19.4	81.8 ± 31.6	0.01
Chronic kidney disease, *n (%)*	145 (3.1)	121 (8.8)	<0.001
In-hospital acute medications			
Aspirin, *n (%)*	4598 (98.9)	1313 (95.7)	<0.001
Clopidogrel, *n (%)*	4417 (94.9)	1146 (83.5)	<0.001
Unfractioned heparin, *n (%)*	3149 (67.7)	617 (44.9)	<0.001
LMWH, *n (%)*	1235 (26.6)	452 (32.9)	<0.001
Fondaparinux, *n (%)*	120 (2.6)	50 (3.6)	0.08
B-blockers, *n (%)*	1100 (23.7)	217 (15.8)	<0.001
ACE-inhibitors, *n (%)*	1204 (25.9)	222 (16.2)	<0.001

BP, blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LMWH, Low molecular weight heparins; ACE, angiotensin-converting-enzyme.

Table S4. Multivariate analysis of factors associated with 30-day all-cause mortality in patients presenting to hospital within 48 hours

	OR	95%CI	*P*-value
Women	1.61	1.27-2.05	<0.001
Age	1.06	1.05-1.07	<0.001
Hypercholesterolemia	0.99	0.94-1.03	0.70
Diabetes	1.07	0.99-1.14	0.052
Hypertension	1.02	0.92-1.12	0.75
Current smoker	1.05	0.97-1.14	0.24
Family history of CAD	1.06	1.01-1.11	0.012
Atypical chest pain	1.03	0.99-1.06	0.13
Heart rate at admission (per 1-SD increment*)	1.38	1.21-1.57	<0.001
Systolic blood pressure at admission (per 1-SD increment*)	0.57	0.51-0.63	<0.001
Prior angina pectoris	0.85	0.59-1.23	0.39
Prior myocardial infarction	1.07	0.74-1.54	0.69
Prior PCI/CABG	1.51	1.08-2.13	0.016
Prior heart failure	1.20	0.71-2.02	0.48
Prior stroke	1.99	1.32-3.00	0.001

Chronic kidney disease	1.35	1.18-1.53	<0.001
Time to presentation, per 1-hours increased	1.02	1.01-1.03	0.001

*SDs for heart rate and systolic blood pressure are 23 b.p.m. and 25 mmHg.

CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table S5. Comparison of pre-hospital delays in patients who required and did not require transfer to a PCI capable hospital

	Men	Women	*P*-value
Median delays in patients who required transfer from a PCI non capable to a PCI capable hospital			
Time from first medical contact to hospital presentation (min), median (IQR)	150 (105-285)	167.5 (110-232.5)	0.95
Time to presentation (min), median (IQR)	360 (180-1076)	400 (205-1025)	0.50
Median delays in patients transferred by EMS ambulance directly to a PCI capable hospital			
Time from first medical contact to hospital presentation (min), median (IQR)	45.5 (35-70)	70 (44-106.5)	0.001
Time to presentation (min), median (IQR)	180 (95-430)	210 (120-725)	0.028

EMS, emergency medical services; IQR, interquartile range; PCI, percutaneous coronary intervention

Table S6. Categorical variables: impact of various medications on the odds of mortality for women.

	OR (95% CI)	P value
Model 1: Overall study population adjusted for demographic and clinical factors		
30-day all-cause mortality	1.58 (1.27-1.97)	<0.001
Model 2: Model 1 including aspirin		
30-day all-cause mortality	1.57 (1.26-1.96)	<0.001
Model 3: Model 1 including aspirin and/or clopidogrel		
30-day all-cause mortality	1.57 (1.26-1.96)	<0.001
Model 4: Model 1 including unfractioned heparin		
30-day all-cause mortality	1.58 (1.27-1.97)	<0.001
Model 5: Model 1 including β blockers		
30-day all-cause mortality	1.57 (1.26-1.95)	<0.001
Model 6: Model 1 including ACE inhibitors		
30-day all-cause mortality	1.57 (1.26-1.95)	<0.001

ACE, angiotensin-converting-enzyme.

Table S7. Interaction test between time to presentation of one hour or less (reference group) and delay of 12 hours or more

	OR	95%CI	*P*-value
Women	1.43	1.03-1.98	0.032
Delay of 12 hours or more	2.20	1.43-3.42	<0.001
Age	1.06	1.05-1.08	<0.001
Hypercholesterolemia	1.02	0.96-1.07	0.43
Diabetes	0.98	0.90-1.07	0.70
Hypertension	0.97	0.82-1.16	0.78
Current smoker	0.96	0.85-1.09	0.56
Family history of CAD	0.99	0.93-1.07	0.92
Atypical chest pain	1.02	0.96-1.08	0.45
Heart rate at admission (per 1-SD increment*)	1.37	1.14-1.65	0.001
Systolic blood pressure at admission (per 1-SD increment*)	0.59	0.51-0.68	<0.001
Prior angina pectoris	0.79	0.49-1.29	0.35
Prior myocardial infarction	1.03	0.64-1.66	0.89
Prior PCI/CABG	1.12	0.68-1.84	0.66
Prior heart failure	0.81	0.39-1.67	0.56
Prior stroke	1.76	1.02-3.04	0.043
Chronic kidney disease	1.54	1.22-1.93	<0.001

*SDs for heart rate and systolic blood pressure are 23 b.p.m. and 25 mmHg.

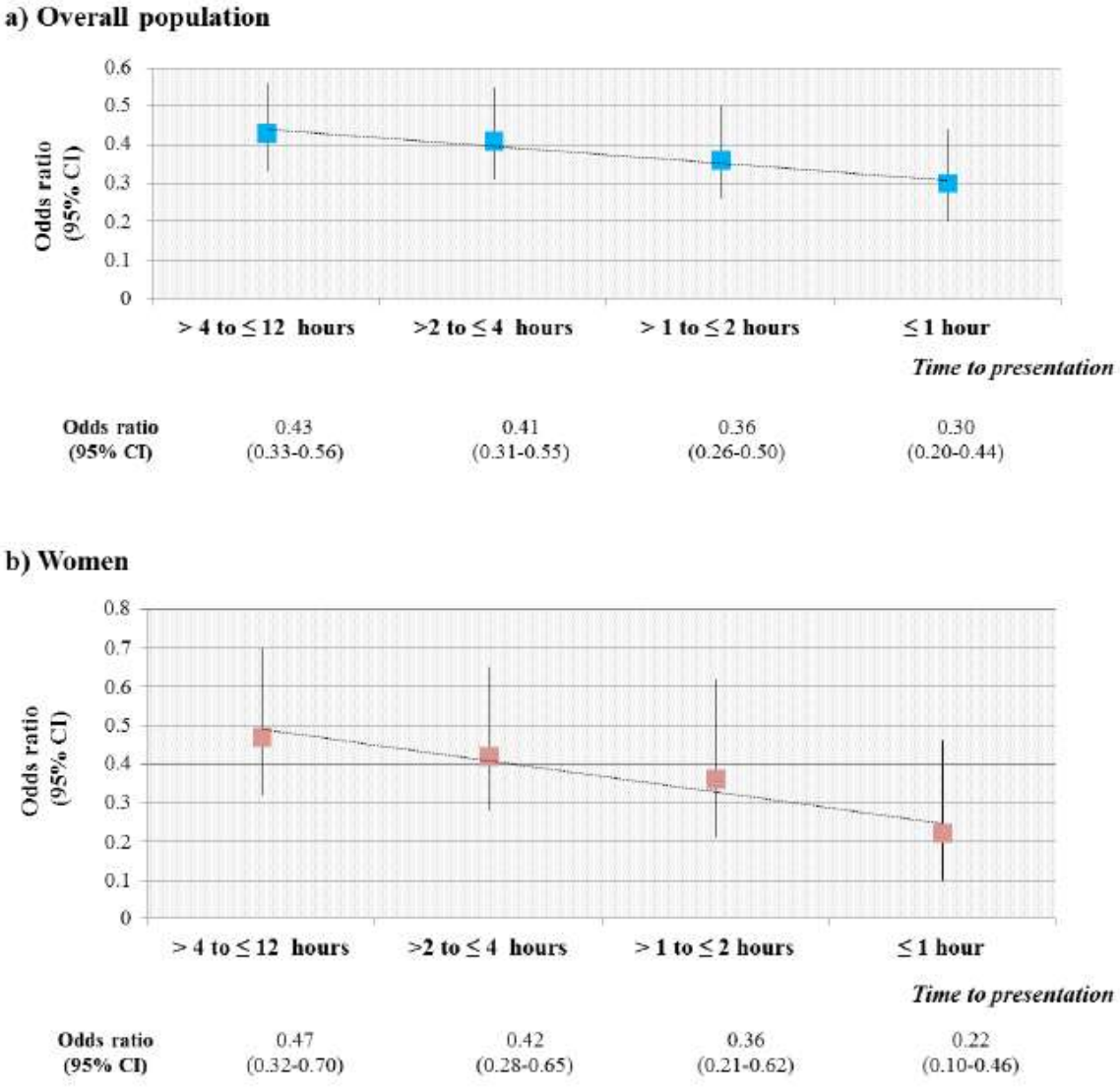
CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table S8. Cardiogenic shock across the designated time delay cohorts. Rates are stratified by sex: women versus men.

	Cardiogenic shock rates, n (%)			Unadjusted		Adjusted*	
	Men (N=2820)	**Women (N=1183)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Overall study population,	145(5.1)	102(8.6)	<0.001	1.74(1.33-2.26)	<0.001	1.56(1.18-2.05)	0.001
Time to presentation > 12 hours	46(6.2)	42(11.2)	0.004	1.89(1.22-2.93)	0.004	1.68(1.06-2.66)	0.026
Time to presentation > 4 to ≤ 12 hours	37(5.9)	27(10.3)	0.023	1.81(1.07-3.04)	0.025	1.80(1.04-3.14)	0.037
Time to presentation > 2 to ≤ 4 hours	26(4.2)	17(6.4)	0.16	1.55(0.82-2.91)	0.17	1.41(0.74-2.69)	0.30
Time to presentation > 1 to ≤ 2 hours	21(4.4)	10(6.2)	0.35	1.44(0.66-3.12)	0.35	1.22(0.55-2.73)	0.62
Time to presentation ≤ 1 hour	15(4.0)	6(5.0)	0.64	1.26(0.48-3.31)	0.64	1.21(0.45-3.28)	0.70

*Adjusted for demographic and clinical factors

Figure S1. Odds of 30-day mortality according to time to presentation in overall population (*panel a*) and in women (*panel b*); reference group: patients with time to presentation of more than 12 hours. CI: confidence intervals



Delayed Care and Mortality Among Women and Men With Myocardial Infarction

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