

# Age-Related Sex Differences in Clinical Presentation, Management, and Outcomes in ST-Segment–Elevation Myocardial Infarction: Pooled Analysis of 15 532 Patients From 7 Arabian Gulf Registries

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**Background**—No studies from the Arabian Gulf region have taken age into account when examining sex differences in ST-segment–elevation myocardial infarction (STEMI) presentation and outcomes. We examined the relationship between sex differences and presenting characteristics, revascularization procedures, and in-hospital mortality after accounting for age in patients hospitalized with STEMI in the Arabian Gulf region from 2005 to 2017.

**Methods and Results**—This study was a pooled analysis of 31 620 patients with a diagnosis of acute coronary syndrome enrolled in 7 Arabian Gulf registries. Of these, 15 532 patients aged  $\geq 18$  years were hospitalized with a primary diagnosis of STEMI. A multiple variable regression model was used to assess sex differences in revascularization, in-hospital mortality, and 1-year mortality. Odds ratios and 95% CIs were calculated. Women were, on average, 8.5 years older than men (mean age: 61.7 versus 53.2 years; absolute standard mean difference: 68.9%). The age-stratified analysis showed that younger women (aged  $< 65$  years) with STEMI were more likely to seek acute medical care and were less likely to receive thrombolytic therapies or primary percutaneous coronary intervention and guideline-recommended pharmacotherapy than men. Women had higher crude in-hospital mortality than men, driven mainly by younger age (46–55 years, odds ratio: 2.60 [95% CI, 1.80–3.7];  $P < 0.001$ ; 56–65 years, odds ratio: 2.32 [95% CI, 1.75–3.08];  $P < 0.001$ ; and 66–75 years, odds ratio: 1.79 [95% CI, 1.33–2.41];  $P < 0.001$ ). Younger women had higher adjusted in-hospital and 1-year mortality rates than younger men ( $P < 0.001$ ).

**Conclusions**—Younger women (aged  $\leq 65$  years) with STEMI were less likely to receive guideline-recommended pharmacotherapy and revascularization than younger men during hospitalization and had higher in-hospital and 1-year mortality rates. (*J Am Heart Assoc.* 2020;9:e013880. DOI: 10.1161/JAHA.119.013880.)

**Key Words:** acute coronary syndrome • hospitalization • Middle East • mortality • myocardial infarction • sex • STEMI

Cardiovascular disease is the leading cause of morbidity and mortality, and women have worse outcomes after acute coronary syndrome (ACS) than men.<sup>1,2</sup> Over the past decade, emerging findings have revealed sex-specific differences in ACS regarding clinical presentation, pathophysiology, diagnosis, and management in women.<sup>3–12</sup> These major gaps are further compounded by the underrepresentation of women in cardiovascular clinical trials.<sup>10</sup> Studies have shown

that women with ST-segment–elevation myocardial infarction (STEMI) have worse short- and long-term outcomes than men.<sup>12–17</sup> Some prognostic factors include older age at presentation, more comorbidities, and the presence of atypical symptoms, which might explain the delay in seeking treatment of women presenting with STEMI.<sup>3,7,12,15–20</sup> These atypical symptoms can be further associated with the delay in diagnosis and management and thus worse clinical outcomes.

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## Clinical Perspective

### What Is New?

- Women receive guideline-recommended pharmacotherapies at hospital discharge less frequently than men.
- In particular, younger women (aged  $\leq 65$  years) with ST-segment-elevation myocardial infarction (STEMI) were less likely to receive guideline-recommended pharmacotherapy and revascularization than younger men during hospitalization and had higher in-hospital and 1-year mortality rates.
- These findings suggest both sex- and age-specific influences on STEMI and provide a possible explanation for sex differences in STEMI outcomes.

### What Are the Clinical Implications?

- Our pooled analysis of the 7 major acute coronary syndrome registries in the Arabian Gulf region from 2005 to 2017 suggests that young women with STEMI are a unique high-risk group that presents a diagnostic challenge for clinicians.
- Although women and men with STEMI derive similar treatment effects, beta-blockers and statins at discharge are still underprescribed for women.

Previous registries from the Arabian Gulf countries (Kuwait, Qatar, Bahrain, United Arab Emirates, Oman, Yemen, and Saudi Arabia) have included STEMI and non-ST-segment-elevation myocardial infarction (NSTEMI) patients and have shown that women presenting with ACS have higher rates of in-hospital mortality than men.<sup>3,12,21–23</sup> Examining potential age–sex disparities in STEMI outcomes in the Gulf region is important because the currently published data are limited by small sample sizes among the different age subgroups of women versus men. Therefore, we sought to examine the relationship between sex differences and presenting characteristics, revascularization procedures, and in-hospital mortality among the different age groups in patients hospitalized with STEMI in a pooled analysis of the 7 major ACS registries in the Arabian Gulf region from 2005 to 2017.

## Methods

The registry data will not be made available, but STEMI-specific data will be made available on request from the corresponding author.

## Data Source

All 7 ACS registries had a prospective consecutive study design. The study cohort consisted of records of patients hospitalized with ACS in 7 Arabian Gulf countries from 2005 to 2017.<sup>3,21,24–27</sup> The overview of the individual

studies is summarized in Table 1. Two of 7 studies were national registries (Saudi Arabia and Kuwait) and used standard definitions according to published American College of Cardiology/European Society of Cardiology (ACC/ESC) guidelines.<sup>28–35</sup> The databases were merged using a standard uniform coding strategy after an extensive review of the original coding system of each registry. Data related to patient characteristics; clinical presentation; management during hospital stay, including medications, reperfusion therapy and procedures, outcomes, and discharge medications; in-hospital mortality; and 1-year mortality were included in the study.

Each registry was approved by the ethics committee at its respective institution and were developed according to the Declaration of Helsinki. Because the patient information was collected anonymously, institutional review boards waived the need for individual informed consent.

## Study Population

From 2005 to 2017, a total of 31 620 patients with a diagnosis of ACS were enrolled in 7 Arabian Gulf registries. Of these, 15 532 patients aged  $\geq 18$  years were hospitalized with a primary diagnosis of STEMI.

## Study Variables

For the analysis, we collected the patient characteristics, baseline risk profile, medical history at presentation, initial assessment and management, in-hospital investigation and clinical management, all-cause in-hospital mortality, and 1-year mortality. Age was stratified into subgroups as follows: 18 to 45, 46 to 55, 56 to 65, 66 to 75, and  $>75$  years.<sup>18,36</sup>

## Statistical Analysis

Sex was compared for clinical characteristics; clinical presentation; management during hospital stay, including medications, reperfusion therapy and procedures, and in-hospital and discharge medications used; all-cause in-hospital mortality; and 1-year mortality. Categorical data were summarized with absolute numbers and percentages. Numeric data were summarized with mean  $\pm$  SD. Baseline characteristics of men and women were compared using the Pearson chi-square test or Fisher exact test for categorical variables. The Student *t* test or Mann–Whitney *U* test was used for continuous variables. In addition, we computed absolute standardized differences (ASDs) to compare the baseline characteristics with sex. The ASD is calculated as the difference in means or proportions divided by a pooled estimate of the SD and is reported in percentages. ASD is not as sensitive as traditional

**Table 1.** Overview of Observational ACS Registries in the Arabian Gulf Countries From 2005 to 2017 (31 620 ACS Patients)

	SPACE	Gulf RACE	Gulf RACE-2	Gulf COAST	Gulf RACE-3	Kuwait REPERFUSE	STARS
ACS patients, n (%)	5055 (15.9)	8176 (25.8)	7930 (25)	4061 (12.8)	2928 (9.2)	1237 (3.9)	2233 (7)
No. of hospitals	17	64	65	29	36	7	50
Published (reference)	Yes <sup>24</sup>	Yes <sup>21</sup>	Yes <sup>3</sup>	Yes <sup>25</sup>	Yes <sup>26</sup>	No	Yes <sup>27</sup>
PCI hospitals, %	71	20	43	31	61	43	40
Countries	KSA	Kuwait, Qatar, Bahrain, UAE, Oman, Yemen	KSA, Qatar, Bahrain, UAE, Oman, Yemen	Kuwait, Bahrain, UAE, Oman	KSA, Kuwait, Qatar, Bahrain, UAE, Oman	Kuwait	KSA
Baseline recruitment period (mo)	2005–2007 (24)	2006–2007 (6)	2008–2009 (9)	2012–2013 (12)	2014–2015 (12)*	2014–2015 (12) <sup>†</sup>	2015–2017 (21) <sup>‡</sup>
Inclusion criteria	≥18 y, STEMI, NSTEMI, UA	≥18 y, STEMI, NSTEMI, UA	≥18 y, STEMI, NSTEMI, UA	≥18 y, STEMI, NSTEMI, UA, Gulf citizen	≥18 y, STEMI within 24 h of symptom onset	≥18 y, STEMI who received reperfusion	≥18 y, STEMI, NSTEMI
STEMI patients (N=15 532), n (%)	2097 (13.5)	3200 (20.6)	3613 (23.2)	1015 (6.5)	2928 (18.8)	1208 (7.7)	1471 (9.4)
In-hospital outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1-mo follow-up, n (%)	No	No	3033 (83.9)	981 (96.6)	No	1208 (100)	888 (60.3)
1-y follow-up, n (%)	No	No	2780 (76.9)	925 (91.1)	No	1176 (97.3)	716 (48.6)

ACS indicates acute coronary syndrome; Gulf COAST, Gulf Locals With Acute Coronary Syndrome Events Registry; Gulf RACE, Gulf Registry of Acute Coronary Events; KSA, Kingdom of Saudi Arabia; Kuwait REPERFUSE, Reperfusion in ST-Segment–Elevation Myocardial Infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SPACE, Saudi Project for Assessment of Coronary Events; STARS, Saudi Acute Myocardial Infarction Registry; STEMI, ST-segment–elevation myocardial infarction; UA, unstable angina; UAE, United Arab Emirates.

\*January 2014 to January 2015.

<sup>†</sup>November 2014 to November 2015.

<sup>‡</sup>Ongoing follow-up.

significance testing to sample size and is useful for identifying clinically meaningful differences (ASD >10%).<sup>37</sup>

Logistic multiple variable regression models were used to assess sex differences in revascularization, in-hospital mortality, and 1-year mortality. Crude and adjusted odds ratios (ORs) with 95% CIs were calculated with men as the reference group. Adjustments were performed for sociodemographics (age, ethnicity), the presence of cardiovascular risk factors (diabetes mellitus, obesity [body mass index >25], hypertension, hypercholesterolemia, and smoking), hospital-level characteristics (echocardiogram and Killip class), revascularization therapy (a history of percutaneous coronary intervention [PCI] or coronary artery bypass grafting), a history of myocardial infarction or stroke, and the time from symptom onset to arrival at the emergency department (ED). Two-tailed tests were used, and  $P < 0.001$  was considered statistically significant. All analyses were performed using SAS/STAT software v9.2 (SAS Institute).

## Results

Of the 15 532 patients aged ≥18 years hospitalized with STEMI in the 7 Gulf registries from 2005 to 2017, 2033 (29.7%) were women. Women were, on average, 8.5 years older than men (mean age: 61.7 versus 53.2 years; ASD: 68.9%). The presence of diabetes mellitus, hypertension, hypercholesterolemia, prior stroke, heart failure, and myocardial infarction was significantly higher in women (ASD >10% for all). However, complaints of chest pain (87% versus 94%), Killip class I (73.8% versus 83.3%), PCI (9.1% versus 11.5%), time from symptom onset to hospital arrival (<3 hours: 41.3% versus 53.3%), ED-to-needle time (<30 minutes: 21.1% versus 29.2%), and ED-to-balloon time (<90 minutes: 46.3% versus 62.5%) were lower in women than in men (Table 2). Age-stratified analysis showed more cardiovascular risk factors for STEMI in women aged 56 to 65 years than men: higher body mass index (≥25; 72.1% versus 64.5%), hypercholesterolemia (40.6% versus 30.4%),

**Table 2.** Baseline Demographics, Comorbidities, and Other Patient Characteristics in Women Versus Men With STEMI

	Total (N=15 532)	Men (n=13 499)	Women (n=2033)	P Value	ASD, %
Age, y, mean±SD	54.38±12.38	53.27±11.96	61.73±12.60	<0.001	68.9
Age group, y					
18–45	3862 (24.8)	3649 (27)	213 (10.4)	<0.001	67.24
46–55	5115 (32.9)	4669 (34.6)	446 (21.9)		
56–65	3790 (24.4)	3156 (23.3)	634 (31.2)		
66–75	1942 (12.5)	1455 (10.7)	487 (23.9)		
≥75	823 (5.3)	570 (4.2)	253 (12.4)		
Body mass index*					
≤24.99	4988 (34.5)	4411 (35.1)	577 (30.7)	<0.001	9.36
≥25	9451 (65.4)	8150 (64.8)	1301 (69.2)		
Ethnicity					
Arab	9031 (58.1)	7263 (53.8)	1768 (86.9)	<0.001	79.67
Non-Arab	6501 (41.86)	6236 (46.20)	265 (13.03)		
Type of STEMI*					
Anterior	7455 (53.9)	6581 (54.4)	874 (50.5)	<0.001	9.33
Inferior	5538 (40)	4811 (39.8)	727 (42)		
Other	821 (5.9)	692 (5.7)	129 (7.4)		
History of MI angina	3051 (19.6)	2567 (19)	484 (23.8)	<0.001	11.7
History of PCI	892 (5.7)	778 (5.7)	114 (5.6)	0.807	0.58
History of CABG	1379 (8.9)	1268 (9.4)	111 (5.4)	<0.001	15.07
History of heart failure	199 (2.2)	150 (1.9)	49 (4.1)	<0.001	13.16
History of stroke	523 (3.3)	378 (2.8)	145 (7.1)	<0.001	20.15
History of chronic renal failure	211 (1.5)	154 (1.3)	57 (3.3)	<0.001	13.54
Diabetes mellitus	6108 (39.5)	4966 (36.9)	1142 (56.5)	<0.001	40.07
Hypertension	5991 (38.7)	4793 (35.6)	1198 (59.2)	<0.001	48.71
Hypercholesterolemia	3933 (26.6)	3263 (25.4)	670 (34.4)	<0.001	19.83
Current or ex-smoking	8930 (57.5)	8432 (62.4)	498 (24.5)	<0.001	82.91
Chief complaint					
Chest pain	13 855 (93.1)	12 174 (94)	1681 (87)	<0.001	24.22
Cardiac arrest	116 (0.7)	92 (0.7)	24 (1.2)		
Other	903 (6)	677 (5.2)	226 (11.7)		
Killip class					
I	12 466 (82)	11 004 (83.3)	1462 (73.8)	<0.001	23.52
II/III	2267 (14.9)	1848 (14)	419 (21.1)		
IV	460 (3)	360 (2.7)	100 (5)		
Echo options					
Normal LV function	3550 (25.5)	3131 (25.8)	419 (23.2)	<0.001	11.48
Mild LV dysfunction	5852 (42.1)	5133 (42.4)	719 (39.8)		
Moderate LV dysfunction	2996 (21.5)	2545 (21)	451 (24.9)		
Severe LV dysfunction	1505 (10.8)	1287 (10.6)	218 (12)		
Elective PCI	1588 (10.9)	1419 (11.1)	169 (9.1)	0.010	6.59

Continued

Table 2. Continued

	Total (N=15 532)	Men (n=13 499)	Women (n=2033)	P Value	ASD, %
CABG	382 (2.6)	333 (2.6)	49 (2.7)	0.923	0.24
Ambulance	3444 (23.3)	2992 (23.2)	452 (23.8)	0.565	2.11
Symptom-to-hospital-arrival time					
<3 h	6390 (51.9)	5789 (53.3)	601 (41.2)	<0.001	28.76
3–12 h	4553 (37)	3945 (36.3)	608 (41.7)		
>12–24 h	1361 (11)	1114 (10.2)	247 (16.9)		
Symptom-to-ED time, min, mean±SD	170.0±257	164.0±248.5	225.0±355.5	<0.001	29.2
ED-to-ECG time, min, mean±SD	9.00±10	9.00±10	10.00±12	<0.001	16.99
ED-to-ECG time <10 min	6010 (51)	5407 (52.1)	603 (42.8)	<0.001	19.26
ED-to-needle time, min, mean±SD	40.00±44	40.00±43	46.00±50	<0.001	21.86
ED-to-needle time <30 min	1942 (28.3)	1788 (29.1)	154 (21.1)	<0.001	18.52
ED-to-balloon time, min, mean±SD	75.00±63	75.00±61	94.00±93	<0.001	31.83
ED-to-balloon time <90 min	1865 (61)	1733 (62.5)	132 (46.3)	<0.001	32.18

Data are shown as n (%) except as noted. LV dysfunction: mild is 40–50% ejection fraction, moderate is 30–40% ejection fraction, and severe is <30% ejection fraction. ASD indicates absolute standardized difference (calculated as differences in means or proportions divided by a pooled estimate of the standard difference); CABG, coronary artery bypass grafting; ED, emergency department; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

\*Some missing data,  $P<0.001$  was considered to be statistically significant.

diabetes mellitus (61.8% versus 45.6%), and hypertension (61.6% versus 44.0%; Table 3).

The women with STEMI (aged 18–45 years) were later in presentation (80.8% versus 62.3%) and less likely to receive thrombolytic therapy (40% versus 28.3%) and primary PCI (17% versus 24.6%) than men. The rates of administration of antiplatelets (76.8% versus 83.3%) and glycoprotein IIb/IIIa inhibitors (12.8% versus 19.8%) were lower in women than in men aged 56–65 years. Furthermore, women were less likely to receive guideline-recommended oral therapies at hospital discharge than men across all age groups (Table 4).

The age-stratified analysis also showed that the use of revascularization in women versus men increased with increasing age groups (Table 5). Among patients with STEMI undergoing revascularization, women aged <65 years were less likely to receive revascularization during hospitalization. After adjusting for demographic features, patient characteristics and comorbidities showed that the lower odds of use of revascularization in women than men decreased with increased age ( $P=0.013$ , aged 46–55 years;  $P=0.002$ , aged 56–65 years;  $P=0.128$ , aged 66–75 years).

### In-Hospital Outcomes

Women had higher crude in-hospital mortality than men. The higher in-hospital mortality in women was driven by younger age (46–55 years, OR: 2.61 [95% CI, 1.80–3.7];  $P<0.001$ ; 56–65 years, OR: 2.32 [95% CI, 1.75–3.08];  $P<0.001$ ). This association between female sex and in-hospital mortality was

significant after adjusting for age, baseline characteristics, and comorbidities (46–55 years, adjusted OR: 2.28 [95% CI, 1.44–3.61];  $P<0.001$ ; 56–65 years, adjusted OR: 1.89 [95% CI, 1.34–2.64];  $P<0.001$ ; Table 5). Additional stepwise adjustment for the use of revascularization showed a significant association of female sex with in-hospital mortality in the age subgroups 46 to 55 years ( $P=0.005$ ) and 56 to 65 years ( $P=0.003$ ).

### One-Year Mortality

Younger women (aged  $\leq 65$  years) were more than twice at risk of 1-year mortality than younger men ( $P<0.001$ ). For older patients (aged >65 years), women had a 59% higher risk of 1-year mortality than men. After adjusting for demographics, baseline characteristics, and comorbidity, female sex still had higher 1-year mortality than male sex (aged  $\leq 65$  years, OR: 1.89 [95% CI, 1.38–2.58]; aged >65 years, OR: 1.58 [95% CI, 1.12–2.23]). This excess mortality was still persistent in young women (aged  $\leq 65$  years) after adjusting for revascularization and the time from symptom onset to arrival at the ED (Table 6).

### Discussion

This pooled analysis of 7 ACS registries represents the first study to assess the relationship of age-stratified sex differences in the clinical presentation, management, and in-hospital

**Table 3.** Age-Stratified Prevalence of Comorbidities in Women Versus Men With STEMI

	18–45 y			46–55 y			56–65 y			66–75 y			≥75 y		
	Men, n (%)	Women, n (%)	ASD, %	Men, n (%)	Women, n (%)	ASD, %	Men, n (%)	Women, n (%)	ASD, %	Men, n (%)	Women, n (%)	ASD, %	Men, n (%)	Women, n (%)	ASD, %
Current/ex-smoking	2596 (71.1)	50 (23.4)	108.66	3082 (66)	121 (27.1)	84.63	1789 (56.6)	152 (23.9)	70.73	719 (49.4)	113 (23.2)	56.65	246 (43.1)	62 (24.5)	40.21
Body mass index															
≤24.99	1215 (35.6)	56 (27.8)	16.84	1389 (32.1)	120 (28.7)	7.4	1041 (35.4)	160 (27.8)	16.49	512 (37.9)	157 (34.4)	7.28	244 (47.5)	84 (36.8)	21.84
≥25	2191 (64.3)	145 (72.1)		2958 (67.9)	298 (71.3)		1894 (64.5)	415 (72.1)		838 (62)	299 (65.5)		269 (52.4)	144 (63.1)	
Hypercholesterolemia	647 (18.8)	42 (20.6)	4.48	1138 (25.6)	142 (33.5)	17.26	917 (30.4)	246 (40.6)	21.44	427 (30.6)	169 (35.7)	10.8	134 (24.2)	71 (29.8)	12.64
Mi/angina	449 (12.3)	38 (17.8)	15.52	846 (18.1)	85 (19)	2.41	689 (21.8)	162 (25.5)	8.76	419 (28.8)	133 (27.3)	3.31	164 (28.7)	66 (26.1)	6.02
PCI	139 (3.8)	4 (1.9)	0.147	266 (5.7)	14 (3.1)	0.024	223 (7.1)	42 (6.6)	1.68	118 (8.1)	37 (7.6)	0.749	32 (5.6)	17 (6.8)	4.75
CABG	265 (7.3)	7 (3.3)	0.027	478 (10.27)	27 (6.1)	0.005	385 (12.2)	40 (6.3)	20.59	106 (7.3)	25 (5.1)	0.108	34 (5.9)	12 (4.7)	5.25
Diabetes mellitus	856 (23.5)	85 (39.9)	35.64	1807 (38.8)	264 (59.6)	42.41	1433 (45.6)	388 (61.8)	33.11	655 (45.2)	284 (58.8)	27.34	215 (38.1)	121 (47.8)	19.7
Hypertension	765 (21)	88 (42.1)	46.52	1664 (35.7)	241 (54.2)	37.83	1385 (44)	389 (61.6)	35.9	714 (49.3)	312 (64.4)	30.89	265 (46.6)	168 (66.4)	40.65
Heart failure	11 (0.5)	0	0.432	28 (1)	8 (3.1)	0.004	47 (2.6)	18 (4.9)	12.32	45 (5.3)	19 (6.44)	4.8	19 (5.3)	4 (2.8)	12.48
Stroke	23 (0.6)	7 (3.3)	19.23	70 (1.5)	21 (4.7)	18.68	119 (3.7)	44 (6.9)	14.14	103 (7.1)	41 (8.5)	5.23	63 (11)	32 (12.8)	5.39
Chronic renal failure	14 (0.4)	0	0.372	25 (0.6)	7 (1.9)	11.62	48 (1.7)	20 (3.7)	12.23	39 (3.2)	18 (4.3)	5.91	28 (5.9)	12 (6)	0.18

P values (<0.001) are for men and women within age category. ASD indicates absolute standardized difference; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

**Table 4.** Age-Stratified Prevalence of In-Hospital Management and Medications Used in Women Versus Men for STEMI

	18-45 y			46-55 y			56-65 y			66-75 y			≥75 y				
	Men, n (%)	Women, n (%)	P Value	ASD, %	Men, n (%)	Women, n (%)	P Value	ASD, %	Men, n (%)	Women, n (%)	P Value	ASD, %	Men, n (%)	Women, n (%)	P Value	ASD, %	
Thrombolytic therapy given	1959 (56.6)	99 (49.5)	0.048	14.3	2437 (55.1)	200 (47.6)	0.003	15.11	1415 (47)	251 (43.0)	0.078	7.99	585 (42.9)	192 (42.3)	0.833	1.15	184 (34.2)
Primary PCI done	828 (23.9)	32 (16)	0.010	19.94	1047 (23.7)	75 (17.8)	0.007	14.42	740 (24.6)	99 (16.9)	<0.001	18.84	265 (19.4)	76 (16.7)	0.206	6.96	91 (16.9)
No reperfusion	673 (19.4)	69 (34.5)	<0.001	34.41	936 (21.1)	145 (34.5)	<0.001	30.1	854 (26.3)	233 (39.9)	<0.001	24.61	512 (37.6)	185 (40.8)	0.218	6.65	263 (48.9)
No reperfusion reason																	
Late presentation	411 (62.3)	55 (80.8)	0.006	51.8	609 (66.7)	105 (74.4)	0.032	28.73	570 (66.5)	159 (71.3)	0.244	15.55	334 (67.2)	120 (65.2)	0.880	7.07	158 (62.7)
Missed	36 (5.4)	1 (1.4)			42 (4.6)	6 (4.2)			47 (5.6)	12 (5.3)			23 (4.6)	7 (3.8)			7 (2.7)
Contraindication	34 (5.1)	5 (7.3)			58 (6.3)	13 (9.2)			54 (6.5)	20 (8.9)			48 (9.6)	19 (10.3)			33 (13.1)
Other	178 (27)	7 (10.3)			204 (22.3)	17 (12)			161 (19.3)	32 (14.3)			92 (18.5)	38 (20.6)			54 (21.4)
Medication 24 h																	
Aspirin	3590 (98.8)	209 (98.5)	0.763	2.04	4625 (99.2)	438 (88.8)	0.422	3.67	3098 (98.4)	622 (98.1)	0.500	2.83	1419 (97.8)	478 (98.3)	0.453	4.07	556 (97.9)
Other antiplatelet	3062 (83.9)	168 (78.8)	0.053	12.98	4007 (85.8)	369 (82.7)	0.077	8.49	2629 (83.3)	487 (76.8)	<0.001	16.29	1176 (80.8)	384 (78.8)	0.343	4.92	441 (77.3)
Beta-blockers	2739 (75.4)	155 (73.1)	0.446	5.31	3471 (74.5)	323 (72.9)	0.460	3.65	2207 (70.1)	438 (69.1)	0.601	2.27	956 (65.9)	309 (63.5)	0.355	4.83	376 (66.1)
ACEI/ARB	2632 (72.4)	160 (75.4)	0.328	7.03	3393 (72.7)	335 (75.2)	0.256	5.71	2279 (72.3)	457 (72.2)	0.937	0.34	1072 (73.8)	334 (68.7)	0.029	11.3	402 (70.6)
Statins	3465 (95.3)	200 (94.3)	0.488	4.69	4449 (95.4)	410 (82.5)	0.006	12.24	2969 (94.3)	596 (94)	0.738	1.44	1339 (92.3)	450 (92.6)	0.858	0.94	523 (91.9)
Aldosterone antagonists/spironolactone	77 (6.9)	7 (16.6)	0.017	30.62	112 (8)	12 (11.8)	0.173	12.96	103 (11.4)	15 (11.3)	0.988	0.13	48 (14)	14 (12.2)	0.636	5.19	19 (13.2)
Heparins, UH/LMWH	3220 (88.5)	187 (88.2)	0.876	1.1	4138 (88.7)	404 (80.8)	0.183	6.69	2751 (87.4)	536 (84.5)	0.053	8.2	1240 (85.4)	415 (85.4)	0.996	0.02	486 (85.4)
Glycoprotein IIb/IIIa inhibitors	712 (19.6)	29 (13.6)	0.034	15.93	912 (19.5)	60 (13.4)	0.002	16.46	625 (19.8)	81 (12.7)	<0.001	19.24	228 (15.7)	66 (13.6)	0.268	5.9	79 (13.8)
Medication at discharge																	
Aspirin	3495 (97.3)	197 (94.7)	0.024	13.57	4449 (96.7)	401 (83.2)	<0.001	16.25	2923 (95.2)	550 (90)	<0.001	20.24	1282 (91.4)	403 (87.4)	0.011	13.11	480 (87.6)
Other antiplatelet	2903 (79.5)	163 (76.5)	0.288	7.32	3768 (80.7)	339 (76)	0.017	11.42	2442 (77.3)	430 (67.8)	<0.001	21.54	1054 (72.4)	317 (65.1)	0.002	15.9	377 (66.1)
Beta-blockers	3151 (87.3)	163 (77.6)	<0.001	25.84	3983 (86.4)	332 (77)	<0.001	24.47	2503 (81)	468 (75.8)	0.003	12.75	1080 (76.2)	325 (69.3)	0.003	15.72	402 (73.1)
ACEI/ARB	2918 (80.4)	164 (77.3)	0.275	7.53	3775 (81.3)	346 (78.6)	0.160	6.85	2495 (79.7)	484 (76.8)	0.100	7.07	1114 (77.2)	337 (69.9)	0.001	16.7	404 (71.3)
Statins	3328 (92.3)	197 (93.8)	0.420	5.98	4297 (93.2)	385 (89.3)	0.003	13.79	2825 (91.5)	544 (88.1)	0.008	11.09	1251 (88.3)	386 (82.3)	<0.001	16.95	470 (85.6)
Oral anticoagulant warfarin/dabigatran	64 (2.7)	2 (1.7)	0.482	7.31	96 (3.2)	17 (6.7)	0.003	16.55	66 (3.3)	15 (4.1)	0.441	4.22	30 (3.5)	9 (2.9)	0.646	3.14	13 (4.1)

P values (<0.001) are for men and women within age category. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; UH, unfractionated heparin.

and 1-year mortality rates in patients with STEMI in the Arabian Gulf region. The main findings of our study were as follows. First, women with STEMI had a significantly higher comorbidity burden than men in the same age group. Second, younger women (aged  $\leq 65$  years) were more likely to seek acute medical care and less likely to receive guideline-recommended pharmacotherapy than younger men. Third, significantly higher crude and adjusted in-hospital and 1-year mortality rates were observed in younger women than in younger men.

Sex differences in the baseline characteristics, presentation, and mortality of acute myocardial infarction are well known and described repeatedly in our previous work.<sup>3,9,21–23</sup> Limited studies have focused on STEMI.<sup>12,25,26</sup> Prior studies mainly reported sex differences in short-term mortality, but after adjusting for age, risk factors, and comorbidities, these differences disappeared.<sup>38–40</sup> In our study, we observed that younger women (aged  $\leq 65$  years) showed 2-fold higher in-hospital mortality than younger men, and younger women showed a significantly increased risk of dying in the hospital and at 1-year follow-up even after adjustment for demographics, baseline characteristics, comorbidities, and revascularization. These findings were in accordance with those of other studies, suggesting that sex differences for in-hospital mortality are driven primarily by the young age groups, with women aged  $\leq 55$  years having a significantly increased risk of in-hospital mortality, and those women who survive an acute myocardial infarction having an increased risk of 30-day mortality compared with similarly aged men.<sup>41–45</sup> The GWTCAD (Get With The Guidelines–Coronary Artery Disease) study

of a STEMI cohort showed significantly higher in-hospital mortality among women within the first 24 hours of hospitalization.<sup>46</sup> Indeed, some factors such as differences in baseline cardiovascular risk profile and clinical profile, disparities in treatment, and low use of revascularization may be contributing factors in outcomes after STEMI in younger women. Furthermore, poor prognostic factors among older women, including lack of awareness of symptoms, longer delay in hospital presentation, and, consequently, suboptimal total ischemic time to PCI were often reported.<sup>2,13,19,26,47</sup> From a pathophysiology point of view, women have a higher prevalence of plaque erosion, and men have a higher prevalence of plaque rupture.<sup>48</sup>

Our study data also provided evidence that  $<50\%$  of women received ECG within 10 minutes, suggesting that sex differences exist in the diagnosis of STEMI. Similar findings were identified in international registries, where longer ED-to-ECG times were observed for women than men.<sup>49,50</sup> However, some studies discussed that these sex differences might be due to poor recognition of atypical symptoms by emergency physicians, which can contribute to delays in treatment<sup>49</sup>; difficulties in implementation of procedures, transfer to the catheterization laboratory, and referral-hospital acceptance; and technical challenges for women in comparison with men at PCI sites.<sup>13</sup> In our results, there was a sex-specific delay in ED-to-needle time ( $<30$  minutes) caused by delayed ECG examination that affected the ED-to-balloon time ( $<90$  minutes) in women. In particular, a clinically significant lower proportion of younger women (aged  $<65$  years) received

**Table 5.** Age-Stratified Analysis of Use of Revascularization and In-Hospital Mortality in Women Versus Men With STEMI

Reperfusion	Overall, n (%)	Men, n (%)	Women, n (%)	OR (95% CI)	P Value	Adjusted* OR (95% CI)	P Value	Adjusted† OR (95% CI)	P Value
<b>Revascularization</b>									
18–45 y	2918 (75.5)	2787 (76.3)	131 (61.5)	0.49 (0.371–0.66)	$<0.001$	0.73 (0.524–1.01)	0.059	0.63 (0.426–0.95)	0.025
46–55 y	3757 (73.4)	3482 (74.5)	275 (61.6)	0.55 (0.448–0.67)	$<0.001$	0.74 (0.583–0.94)	0.013	0.70 (0.527–0.94)	0.018
56–65 y	2504 (66)	2153 (68.2)	351 (55.3)	0.58 (0.486–0.69)	$<0.001$	0.72 (0.584–0.88)	0.002	0.70 (0.546–0.91)	0.007
66–75 y	1118 (57.5)	850 (58.4)	268 (55)	0.87 (0.708–1.07)	0.190	0.84 (0.663–1.05)	0.128	0.74 (0.544–0.99)	0.047
$>75$ y	388 (47.1)	274 (48)	114 (45)	0.89 (0.658–1.19)	0.426	0.70 (0.494–0.99)	0.044	0.81 (0.512–1.29)	0.378
<b>In-hospital mortality</b>									
18–45 y	78 (2)	70 (1.9)	8 (3.7)	2.00 (0.949–4.21)	0.069	1.64 (0.642–4.19)	0.301	1.21 (0.402–3.65)	0.732
46–55 y	194 (3.8)	157 (3.3)	37 (8.3)	2.60 (1.793–3.77)	$<0.001$	2.28 (1.444–3.61)	$<0.001$	2.12 (1.261–3.56)	0.005
56–65 y	254 (6.7)	177 (5.6)	77 (12.1)	2.32 (1.751–3.08)	$<0.001$	1.89 (1.346–2.64)	$<0.001$	1.77 (1.211–2.60)	0.003
66–75 y	221 (11.4)	142 (9.7)	79 (16.2)	1.79 (1.331–2.41)	$<0.001$	1.60 (1.141–2.24)	0.006	1.36 (0.912–2.03)	0.131
$>75$ y	136 (16.5)	85 (14.9)	51 (20.1)	1.44 (0.979–2.11)	0.064	1.53 (0.983–2.37)	0.060	1.69 (1.015–2.82)	0.044

Reference group was men.  $P < 0.001$  was considered to be statistically significant. CABG indicates coronary artery bypass grafting; ED, emergency-department; PCI, percutaneous coronary intervention; OR, odds ratio; STEMI, ST-segment-elevation myocardial infarction.

\*Adjusted for age, ethnicity, body mass index, diabetes mellitus, hypertension, smoking, history of myocardial infarction/angina, history of PCI, history of CABG, and history of stroke.

†Adjusted for age, ethnicity, body mass index, diabetes mellitus, hypertension, smoking, history of myocardial infarction/angina, history of PCI, history of CABG, history of stroke, in-hospital revascularization, and symptoms-to-ED time.



**Table 6.** Age-Stratified 1-Year Mortality in Women and Men With STEMI

1-y Mortality	Overall, n (%)	Men, n (%)	Women, n (%)	OR (95% CI)	P Value	Adjusted* OR (95% CI)	P Value	Adjusted <sup>†</sup> OR (95% CI)	P Value
≤65 y	353 (7.8)	276 (6.8)	77 (15.4)	2.48 (1.89–3.26)	<0.001	1.89 (1.38–2.58)	<0.001	1.85 (1.34–2.57)	<0.001
>65 y	224 (20.3)	150 (18.2)	74 (26.2)	1.59 (1.15–2.19)	0.004	1.58 (1.12–2.23)	0.008	1.48 (1.03–2.12)	0.034

Reference group was men.  $P < 0.001$  was considered to be statistically significant. CABG indicates coronary artery bypass grafting; ED, emergency-department; PCI, percutaneous coronary intervention; OR, odds ratio; STEMI, ST-segment-elevation myocardial infarction.

\*Adjusted for age, ethnicity, body mass index, diabetes mellitus, hypertension, smoking, history of myocardial infarction/angina, history of PCI, history of CABG, and history of stroke.

<sup>†</sup>Adjusted for age, ethnicity, body mass index, diabetes mellitus, hypertension, smoking, history of myocardial infarction/angina, history of PCI, history of CABG, history of stroke, in-hospital revascularization, and symptoms-to-ED time.

acute reperfusion therapies (thrombolytic therapies or primary PCI). Although we will not be able to explain the underlying cause, there is a need to focus on quality measures that can prevent delay in younger women in the Arabian Gulf region because a shorter time to reperfusion improves mortality. This could include the implementation of timely ECGs in emergency medical services, STEMI field activation, and direct transport of the patient to catheterization facilities to improve outcomes and to eliminate sex biases. However, we previously showed that only 5% of STEMI patients in Gulf RACE-3 (Gulf Registry of Acute Coronary Events 3) and 25% of the patients with ACS in Gulf RACE-1 and Gulf RACE-2 used emergency medical services in our region.<sup>26,51</sup> In this regard, efforts should be made to improve public awareness about heart disease, particularly among younger women; to educate patients with at least 1 traditional cardiac risk factor following STEMI to utilize emergency medical services; and to regionalize care, which could reduce field delays. Further interventions are needed to encourage men and women with STEMI to seek care promptly; proactive measures should target high-risk groups (younger women) to improve care and survival of women.

Women were generally less frequently prescribed guideline-recommended pharmacotherapies than men during the acute phase and at time of discharge, which is in line with other publications.<sup>52–55</sup> Women derive the same treatment benefit as men from aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, aldosterone antagonists, anticoagulants, and statins. Our results showed that women with STEMI were underprescribed beta-blockers and statins at discharge. The benefits of beta-blockers and statin therapy after STEMI were similar in both women and men (relative risk for major coronary events: 0.81 [95% CI, 0.74–0.89] and 0.82 [95% CI, 0.78–0.85], respectively).<sup>56,57</sup> Further studies are needed to explore the contribution of the underutilization of guideline-recommended pharmacologic therapies in women to mortality outcomes.

Our study has the major strength of a large sample size with statistical power that enabled us to compare women and men among the different age subgroups by pooling data from

7 ACS registries over a 12-year time period. However, as with any other observational study, our study has inherent limitations, such as the possibility of residual measured or unmeasured confounding variables. The data presented in this analysis were from patients who enrolled voluntarily in the registries at participating study hospitals across the Arabian Gulf region from 2005 to 2017; therefore, we cannot generalize our findings to all patients with STEMI, and the patients may appear in >1 registry. The reasons for delay in presentations, the severity of comorbidities, and receipt or not of revascularization could not be ascertained. Last, the 1-year follow-up data were available in only 4 of the 7 pooled ACS registries.

## Conclusions

Women were less likely to receive guideline-recommended pharmacotherapies at hospital discharge than men across all age groups. Younger women (aged ≤65 years) had higher crude and adjusted in-hospital and 1-year mortality rates than younger men. Consequently, interventions that reduce variations in practice at the community, institutional, and regional levels are needed to improve outcomes in women with STEMI, particularly those aged <65 years. Public awareness campaigns targeting women, such as the American Heart Association's Go Red campaign, are urgently needed in the Arabian Gulf region.

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## Disclosures

None.

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