original article

Gender inequality in the clinical outcomes of equally treated acute coronary syndrome patients in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Gender associations with acute coronary syndrome (ACS), remain inconsistent. Gender-specific data in the Saudi Project for Assessment of Coronary Events registry, launched in December 2005 and currently with 17 participating hospitals, were explored.

DESIGN AND SETTINGS: A prospective multicenter study of patient with ACS in secondary and tertiary care centers in Saudi Arabia were included in this analysis.

PATIENTS AND METHODS: Patients enrolled from December 2005 until December 2007 included those presented to participating hospitals or transferred from non-registry hospitals. Summarized data were analyzed.

RESULTS: Of 5061 patients, 1142 (23%) were women. Women were more frequently diagnosed with non ST-segment elevation myocardial infarction (NSTEMI [43%]) than unstable angina (UA [29%]) or ST-segment elevation myocardial infarction (STEMI [29%]). More men had STEMI (42%) than NSTEMI (37%) or UA (22%). Men were younger than women (57 vs 63 years) who had more diabetes, hypertension, and hyperlipidemia. More men had a history of coronary artery disease. More women received angiotensin receptor blockers (ARB) and fewer had percutaneous coronary intervention (PCI). Gender differences in the subset of STEMI patients were similar to those in the entire cohort. However, gender differences in the subset of STEMI showed fewer women given β-blockers, and an insignificant PCI difference between genders. Thrombolysis rates between genders were similar. Overall, in-hospital mortality was significantly worse for women and, by ACS type, was significantly greater in women for STEMI and NSTEMI. However, after age adjustment there was no difference in mortality between men and women in patients with NSTEMI. The multivariate-adjusted (age, risk factors, treatments, door-to-needle time) STEMI gender mortality difference was not significant (OR=2.0, CI: 0.7-5.5; *P*=.14).

CONCLUSION: These data are similar to other reported data. However, differences exist, and their explanation should be pursued to provide a valuable insight into understanding ACS and improving its management.

Coronary artery disease (CAD) is well recognized as a most common cause of death in both women and men in large parts of the industrialized world.[1] Over the past decade, the existence of sex/gender differences in terms of presentation of symptoms, validity of diagnostic tests, in-hospital medication, drug side effects, clinical outcomes, complications, and management of acute coronary syndrome (ACS) are frequently reported in the published reports.[2-5]

The prevalence of ACS diagnosed in emergency departments is lower for women than men,[6] with rates dependent on clinical presentation at the time of admission. The percentage of women diagnosed with ACS can range from 33% to 45%.[7] Furthermore, a smaller percentage of women than men presented with ST-elevation myocardial infarction (STEMI) (secondary to occlusive thrombus), but more presented with unstable angina (reflecting subtotal occlusion).[1,8] Moreover, sex differences in symptoms of ACS exist, which might be explained by differences in anatomic, physiologic, bio-

logic, and psychologic characteristics among them.[3,9]

Previous studies demonstrating important differences in the outcomes of men and women with ACS have focused on the management and the performance of revascularization procedures.[10-12] A systematic review of the diagnosis and treatment of CAD found significant evidence that women admitted to hospital with ACS are less likely to receive aspirin, β-blockers, or thrombolysis; less likely to undergo exercise stress testing; and also are less likely to undergo angiography or revascularization.[13] Although not all studies have found such gender differences, particularly after adjusting for important confounding factors such as age.[14,15]

Several studies are available from Western countries on gender disparities in ACS treatment and outcomes; however, no data is available from Saudi Arabia. Accordingly; our objective was to explore whether gender-related differences exist in the treatment and outcomes of patients presenting with ACS in Saudi Arabia.

PATIENTS AND METHODS

The Saudi Project for Assessment of Coronary Events study is a prospective registry and a quality improvement initiative of all consecutive ACS patients that were admitted to the participating hospitals.[16] Ethical approval was obtained in all participating centers. The diagnosis of the different types of ACS was based on the definitions of the Joint Committee of the European Society of Cardiology/American College of Cardiology (ACC).[16] Serum cardiac biomarkers used to assist in the diagnosis of myocardial injury were measured locally at each hospital's laboratory using its own assays and reference ranges.

Study design and population
ACS patients include those with STEMI, non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). We report here the results of the 2 phases of the study that lasted from December 2005 until December 2007. There were 13 hospitals in phase-I and 17 in phase-II; one third of the hospitals were nontertiary care hospitals with no cardiac catheterization and/or cardiac surgery facilities. The details of these phases were outlined previously.[17]

In summary, phase-I extended over a 1-year period and included baseline registry of process of care, outcomes, and health care services. Subsequently, the overall and individual-hospital results were sent to each hospital to improve on the knowledge-care gap and get a comparison with national practices.

Phase-II extended for another 1 year and data was collected using the Internet (*www.space-ksa.com*).

Overall and individual-hospital results were also provided "real-time" during this on-line phase to all participating hospitals.

Study organization
A case report form (CRF) for each patient with suspected ACS was filled out on hospital admission by assigned physicians working in each hospital using standard definitions, and then was completed throughout the hospital stay. All CRFs were verified by a cardiologist and then sent to the principal coordinating center where the forms were further checked for incomplete data and mistakes before submission for final analysis. To avoid double-counting patients, each patient's national identification number was used. An independent clinical research organization (Dubai Pharmaceutical, Dubai, UAE) was contracted to randomly audit all data collected from 20% of the hospitals in phase-I. Data accuracy was found to be more than 99%.

Case report form data variables
Data collected included the following variables: patients' demographics, medical history, provisional diagnosis on admission and final discharge diagnosis, electrocardiographic findings, laboratory investigations, medical therapy, use of cardiac procedures and interventions, in-hospital outcomes, and mortality.

Statistics
Differences in categorical variables between respective comparison groups were analyzed using the chi-square test or Fisher exact test. Continuous variables were analyzed using a *t* test or Mann-Whitney U test based on the satisfaction of normality assumption. *P* values were reported as 2-sided test results with a 5% level of significance for each test. Multiple logistic regression analysis was used to identify whether gender was an independent predictor of in-hospital mortality. Variables considered for inclusion were baseline demographic characteristics medical history diabetes mellitus, hypertension, hyperlipidemia, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), in-hospital therapies, and door-to-needle-time. All analyses were performed using STATA version 9 (StataCorp LP, United States).

RESULTS

A total of 5061 patients with the diagnosis of ACS were enrolled from 30 hospitals during the period between December 2005 and December 2007. **Table 1** depicts the baseline characteristics of the whole cohort. A total of 77.4% (3919) were men and 22.3% (1142)

Table 1. Baseline characteristics of patients with ACS stratified by gender in Saudi Arabia.

Variables	Overall n=5061 n (%)	Male N=3919(77.4)	Female N=1142 (22.6)	P value
Age (mean [SD])	58.01 (12.9)	56.7 (12.9)	62.5 (11.9)	<.001
Key risk factors				
Diabetes mellitus	2937 (58.1)	2104 (41.6)	835 (73.2)	<.001
Nationality (Saudi)	4167 (82.4)	3104 (61.4)	1063 (93.2)	<.001
Hypertension	2785 (55.3)	1936 (49.5)	849 (75.1)	<.001
Coronary artery disease	718 (14.2)	592 (15.2)	126 (11.2)	.001
PCI	700 (13.8)	543 (13.9)	157 (13.7)	.65
CABG	296 (5.8)	232 (5.9)	64 (5.6)	.36
Smoker	1636 (32.3)	1591 (40.6)	45 (3.9)	<.001
Hyperlipidemia	2086 (45.4)	1526 (39.0)	560 (49.6)	<.001
CVA/TIA	309 (6.1)	228 (5.8)	81 (7.1)	.24
PAD	203 (10.5)	149 (10)	54 (11.5)	.22
Clinical features on presentation				
Systolic BP≤90	148 (3.2)	116 (3.3)	32 (3.0)	.72
Heart rate≥100	679 (14.9)	468 (13.3)	211 (20.2)	<.001
Body mass index	27.6 (6.1)	27.7 (4.3)	29.7 (6.9)	<.001
Ischemic chest pain	3057 (87.6)	2419 (89.3)	638 (81.9)	.4
Atypical chest pain	115 (3.3)	84 (3.1)	31 (4)	.8
Key investigations				
Troponin	3152 (62.5)	2453 (62.9)	699 (61.4)	.21
Coronary angiogram	3403 (67.2)	2658 (67.8)	745 (65.3)	.27
In-hospital treatment				
Aspirin	4935 (97.7)	3826 (97.9)	1109 (97.4)	.19
Clopidogrel	4231 (83.8)	3273 (83.7)	958 (84.1)	.74
-blocker	4120 (81.6)	3206 (82)	914 (80.2)	.18
ACEI	3508 (69.5)	2735 (69.9)	773 (67.9)	.17
ARB	297 (5.9)	183 (4.7)	114 (10.0)	<.001
Statin	4711 (93.3)	3656 (93.5)	1055 (92.6)	.29
PCI	1775 (35.3)	1416 (36.3)	356 (31.6)	.001
CABG	425 (8.4)	332 (8.5)	93 (8.1)	.52
In-hospital outcomes				
Recurrent ischemia	639 (12.6)	473 (12.1)	166 (14.5)	.02
Re-MI	77 (1.5)	54 (1.4)	23 (2.0)	.12
Death	155 (3.0)	96 (2.5)	59 (5.2)	<.001
CHF	520 (10.2)	335 (8.6)	185 (16.2)	<.001

Cardiogenic shock	222 (4.4)	161 (4.1)	61 (5.3)	.07
Major bleeding	68 (1.3)	46 (1.2)	22 (1.9)	.05
Stroke	48 (0.9)	32 (0.8)	16 (1.4)	.07
Discharge diagnosis				
STEMI	2099 (41.5)	1772 (45.2)	327 (28.6)	<.0001
NSTEMI	1844 (36.5)	1357 (34.6)	487 (42.6)	<.0001
UA	1118 (22.1)	790 (20.1)	328 (28.7)	<.0001

SD: Standard deviation, CVA/TIA: cerebrovascular accident/transient ischemic attack, PAD: peripheral artery disease, BP: blood pressure, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, PCI: percutaneous coronary intervention, UA: unstable angina, CABG: coronary artery bypass graft, STEMI: ST-elevation myocardial infarction, NSTEMI: non–ST-elevation myocardial infarction, CHF: congestive heart failure, re-MI: remyocardial infarction.
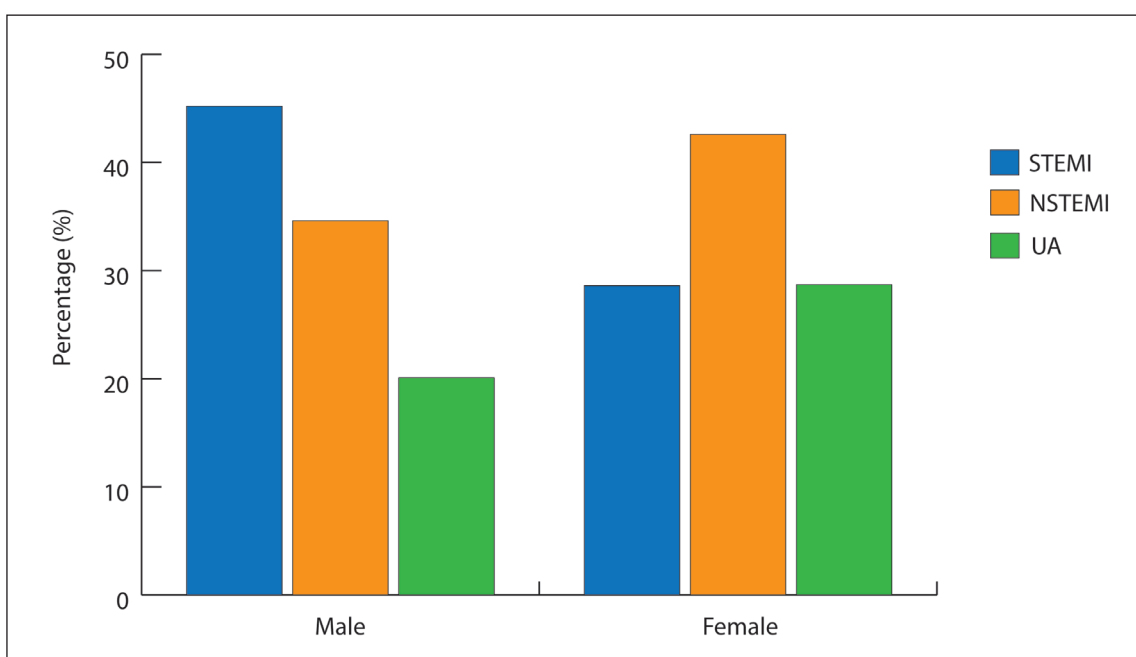
Figure 1. Distribution of gender according to the ACS type.

were women. The mean age of women was 63 years compared with 57 years for men ($P<.001$) (**Table 1**). Women had significantly higher baseline risks like diabetes mellitus, hypertension, hyperlipidemia, higher body mass index and tachycardia in men ($P<.001$ for all comparisons). However, the prevalence of CAD in men was higher than in women (15.2% vs 11.2%; $P=.001$), but there was no difference in the rate of men and women who underwent PCI and CABG surgery without any disparity.

A significant difference in presenting diagnosis based on gender was observed where STEMI was common in male patients (45.2% vs 28.6%, $P<.001$), whereas the NSTEMI (34.6% vs 42.6%; $P<.001$) and UA (20.1% vs 28.7%; $P<.001$) were more common in women patients (**Figure 1**).

There was no significant difference between men and women in terms of symptoms at presentation to hospital (89.3% vs 81.9%; $P=.4$). Women were more likely than men to have more severe clinical abnormalities (i.e., lower systolic BP and higher pulse rate) but less likely than their male peers to have unusual chest pain. The incidence of cerebrovascular accident/transient ischemic attack and peripheral artery disease was not different between the 2 groups. Moreover, key diagnostic investigations like troponin and coronary angiogram were similar in both the genders.

In-hospital medications and clinical outcome comparisons
No significant differences were observed in the administration of aspirin, clopidogrel, angiotensin converting enzyme inhibitors/blockers, β-blocker, and lipid-lowering agents between female and male patients in the hospital. PCI was more significantly performed in men than women (36.3% vs 31.6%; *P*=.001); however, there was no significant difference in the rate of CABG between the 2 groups. The rate of in-hospital death was significantly more in women than men (5.2% vs2.5%; *P*=.02), the rate of congestive heart failure (CHF) was significantly more in women than men (16.2% vs 8.6%, *P*<.001), and the rate of recurrent ischemia was also significantly more in women than men (14.5% vs

12.1%, *P*=.02). Moreover the rate of cardiogenic shock (5.3% vs 4.1%, *P*=.07), stroke (1.4% vs 0.8%, *P*=.07), major bleeding (1.9% vs 1.2%, *P*=.05), and re-MI (re-myocardial infarction) (2.0% vs 1.4%, *P*=.12) were not significantly different between the 2 groups.

Table 2 depicts the demographic, in-hospital treatment, and the outcomes of patients with STEMI. The mean age of women was significantly higher than of men (62.5 vs 56.7, *P*=.001). There was no difference in the use of evidence-based medication or the rate of thrombolytic and primary PCI between the 2 groups. Women had higher in–hospital mortality rate (11% vs 3.3% *P*<.001), higher CHF (20.2% vs 9.8%, *P*<.001), and higher cardiogenic shock rate (11% vs 6.95, *P*=.01)

Table 2. In-hospital medications and clinical outcome comparisons. Comparing baseline characteristics, in-hospital treatment, and outcomes in women and men who were admitted with STEMI.

Variables	Overall n=2099 n (%)	Male N=1772(45.2)	Female N=327 (28.6)	*P* value
Age (mean [SD])	58.01 (12.9)	56.7 (12.9)	62.5 (11.9)	<.001
Clinical features on presentation				
Systolic BP≤90	148 (3.2)	116 (3.3)	32 (3.0)	.72
Heart rate≥100	679 (14.9)	468 (13.3)	211 (20.2)	<.001
In-hospital treatment				
Aspirin	2061 (98.4)	1738 (98.3)	323 (98.8)	.53
Clopidogrel	1681 (80.2)	1420 (80.3)	261 (79.8)	.83
β-blocker	1628 (77.7)	1388 (78.5)	240 (73.4)	.04
ACEI	1560 (74.5))	1316 (74.4)	244 (74.6)	.94
ARB	45 (2.1)	37 (2.1)	8 (2.4)	.68
Statin	1937 (92.5)	1640 (92.8)	297 (90.8)	.22
Thrombolysis	1152 (60.6)	994 (61.3)	158 (56.4)	.10
Primary PCI	425 (8.4)	332 (8.5)	93 (8.1)	.51
DNT (median, IQR)	52 (55)	52 (64)	71 (100)	.035
In-hospital outcomes				
Recurrent ischemia	318 (15.2)	259 (14.6)	59 (18)	.11
Re-MI	49 (2.3)	37 (2.1)	12 (3.7)	.08
Death	95 (5.4)	59 (3.3)	36 (11)	<.001
CHF	240 (11.4)	174 (9.8)	66 (20.2)	<.001
Cardiogenic shock	158 (7.5)	122 (6.9)	36 (11)	.01
Major bleeding	27 (1.3)	22 (1.2)	5 (1.5)	.67
Stroke	30 (1.4)	22 (1.2)	8 (2.4)	.09

SD: Standard deviation, BP: blood pressure, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, PCI: percutaneous coronary intervention, STEMI: ST-elevation myocardial infarction, CHF: congestive heart failure, re-MI: remyocardial infarction, DNT: door-to-needle-time..

Table 3. In-hospital mortality by ACS type.

Variable	OR	95% CI	Age-adjusted OR	95% CI	P value
STEMI	3.5	2.3-5.5	2.5	1.5-3.8	<.001
NSTEMI	2.0	1.2-3.5	1.5	0.97-2.9	.06

ACS: Acute coronary syndrome, STEMI: ST-elevation myocardial infarction, NSTEMI: non–ST-elevation myocardial infarction, OR: odds ratio, CI: confidence interval.

Table 4. Age-adjusted odds ratio (OR)and 95% confidence interval for hospital mortality in women compared to men with ACS in Saudi Arabia for those admitted with STEMI.

Confounder adjusted for	Adjusted OR	P value
Risk factors (age, diabetes mellitus, hypertension, dyslipidemia , CAD, smoking, PCI, and CABG)	2 (1.2-3)	.003
Treatment (aspirin, β-blocker, ACE I, ARB, clopidogrel, statin, and thrombloytic)	2.5 (1.4-4.2)	.001
Age, risk factors, and treatments	2 (1.1-3.4)	.017
Age, risk factors, treatments, and DNT	2 (0.7-5.5)	.14

PCI: Percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, STEMI: ST-elevation myocardial infarction, DNT: door-to-needle time.

than men. However; there was no significant difference in the rate of major bleeding, stroke or re-MI between the 2 groups.

In-hospital mortality

Table 3 depicts the crude and age-adjusted odds ratios (OR) associated with the in-hospital mortality. The crude OR associated with the in-hospital mortality was higher in women 3.5 (95% CI: 2.3-5.5) for SETMI and was 2 (95% CI: 1.2-3.5) for NSTEMI. There was no significant difference in the mortality between the 2 groups in patients with UA. Age-adjusted OR for the in-hospital mortality was higher in women for STEMI 2.5 (95% CI: 1.5-3.8; *P*<.001) and was not significant for NSTEMI OR 1.5 (95% CI: 0.97-2.9; *P*=.060).

Multiple logistic regression models were developed to adjust for potential confounders that may explain the gender variability in mortality (**Table 4**). When we adjusted for baseline characteristics or in-hospital treatments, excess mortality in women was significantly higher (adjusted odd ratio [AOR] 2 [95% CI: 1.2-3; *P*=.003] and AOR 2.5 [95% CI: 1.4-4.2; *P*=.001], respectively). When we adjusted for treatment and risk

factors, excess mortality in women was significantly higher aand AOR was 2 (95% CI: 1.1-3.4; *P*=.017). Adding DNT time, the AOR was no longer significant, i.e., 2 (95% CI: 0.7-5.5; *P*=.14).

DISCUSSION

This study provides information on the demographics, in-hospital treatment, and outcomes of women presenting with ACS compared to men in Saudi Arabia. The main findings of the present study were that the Saudi women developed ACS at higher age, had a higher prevalence of traditional risk factor, equally treated with evidence-based therapies with a significant delay in the administration in these therapies, and had worse in-hospital outcomes than men. Previous reports showed that women had their first cardiac event 6 to 10 years later than men and had higher attributable risk factors.[18]

Furthermore, typically, more women with ACS present without chest pain or discomfort; however, the difference is not universal and prompted[12,19,20] to emphasize that public health symptom messages should not be changed to include lesser chest pain in women. In the present study, neither the lesser frequency of ischemic chest pain nor the slightly greater frequency of atypical chest pain in women compared with men was significant.

Saudi women presented more often with UA and NSTEMI, whereas men had more frequently STEMI, which is in accordance with earlier studies such as GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes), TIMI IIIB (Thrombolysis In Myocardial Infarction), and the Euro Heart Survey.[21-23] These gender-related differences may be accounted for the differences in anatomy, pathophysiology of CAD, and clinical characteristics in women versus men.[21]

Concerning patient management, there is conflicting evidence for a gender-related bias. Several studies documented a clear gender bias in referral to diagnostic procedures and treatment of coronary artery disease.[24-26] American College of Cardiology/American Heart Association guidelines for NSTEMI ACS care at hospital discharge include aspirin, clopidogrel, β-blockers,

ACE inhibitor, lipid-lowering agent, smoking cessation, dietary modification, counseling, and cardiac rehabilitation. In our study, in-hospital medications irrespective of gender followed the protocol treatment guidelines. However, more female patients were prescribed angiotensin receptor blockers compared to men, possibly for renal protection attributing to higher baseline risk factors such as diabetes.[27,28] In addition, no significant differences were noted in the rate of CABG or thrombolytic therapies between the 2 groups; however, the rate of PCI was significantly lower in female patients than male.

Like other reports,[29] our study showed that CHF and recurrent ischemia were more often reported in the female group, whereas no significant gender difference was found in the occurrence of cardiogenic shock, stroke, major bleeding, and re-MI rate. For example, Maynard et al reported a higher incidence of CHF in women ACS patients during hospitalization,[30-32] suggestive of diastolic dysfunction as a large component of the presentation of heart failure in ACS women.[22]

In one of the studies, a subset of women presented with STEMI showed higher rate of in-hospital mortality than men.[7] This difference was attributed to their older age, higher baseline risks, more frequent comorbidities, and less frequent use of revascularization or undertreatment, or restricted to a subgroup of female patients (possibly related to smaller target vessel size, increased vessel tortuosity, and other biological differences).[33-36] Similar to our study several reports from randomized clinical trial (GUSTO, ISIS 3) and lager databases (RESCATE, Washington, NARMI) indicate that women gender is an independent risk factor for CHF, cardiogenic shock and in-hospital mortality after adjusting for age, comorbidities and evidence-based therapies for STEMI. In addition, it is argued that under-referral of women may have been the cause of increased morbidity and mortality in women, particularly associated with PCI procedure.[37,38] However, there was no differ-

ence in rate of referral for PCI in our STEMI between the groups. Moreover, reports indicate that women with STEMI tend to delay seeking medical attention than men (GUSTO 1), upon arrival to the hospital they typically experience further delay in administration of thrombolytic therapy. Jacson et al reported that women waited a mean of 23 minutes longer before receiving thrombolytic therapy than men (112.2 [84.1] vs 89.6 [68.7]) minutes, $P<.1$; median 100 and 75 minutes, women and men, respectively. In our study there was a significant delay in administrating thrombolytic therapy to women, which is not explained by differences in symptoms at presentation (median 52 vs 71 minutes, men and women, respectively; $P=.035$). Adjusting for DTN time did remove the increased in-hospital mortality in women with STEMI.

Limitations

Our data is based on observational registry. The main limitation of such design is nonrandomized nature and unmeasured cofounders. However, well-designed registry data provide valid results. We did not systematically capture the time of onset of symptoms to hospital presentation, which perhaps confounded the findings of this study.

In conclusion, women develop ACS at a higher age in Saudi and have higher attributable baseline risk factors. They predominantly present with NSTEMI and unstable angina. Saudi women with STEMI independently predicted poorer outcomes in terms of CHF, cardiogenic shock, and in-hospital mortality. In our study, this finding is related to delay in the administration of thrombolytic therapy. Hence physicians need to increase the awareness of prompted administration of effective therapy in women with STEMI.

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