

Gender Differences in Clinical Features and In-hospital Outcomes in ST-segment Elevation Acute Myocardial Infarction: From the Korean Acute Myocardial Infarction Registry (KAMIR) Study

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ABSTRACT

Background: Studies have suggested that women are biologically different and that female gender itself is independently associated with poor clinical outcome after an acute myocardial infarction (AMI).

Hypothesis: We analyzed data from the Korean Acute Myocardial Infarction Registry (KAMIR) to assess gender differences in in-hospital outcomes post ST-segment elevation myocardial infarction (STEMI).

Methods: Between November 2005 and July 2007, 4037 patients who were admitted with STEMI to 41 facilities were registered into the KAMIR database; patients admitted within 72 hours of symptom onset were selected and included in this study.

Results: The proportion of patients who had reperfusion therapy within 12 hours from chest pain onset was lower in women. Women had higher rates of in-hospital mortality (8.6% vs 3.2%, $P < .01$), noncardiac death (1.5% vs 0.4%, $P < .01$), cardiac death (7.1% vs 2.8%, $P < .01$), and stroke (1.2% vs 0.5%, $P < .05$) than men. Multivariate logistic regression analysis identified age, previous angina, hypertension, a Killip class \geq II, a left ventricular ejection fraction (LVEF) $<40\%$, and a thrombolysis in myocardial infarction flow (TIMI) grade ≤ 3 after angioplasty as independent risk factors for in-hospital death for all patients; however, female gender itself was not an independent risk factor.

Conclusions: The results of this study show that although women have a higher in-hospital mortality than men, female gender itself is not an independent risk factor for in-hospital mortality.

Introduction

Ischemic heart disease is the leading cause of death worldwide. The prevalence of coronary artery disease is increasing and becoming a major cause of morbidity and mortality in Korea.¹ Acute myocardial infarction (AMI) continues to be a major public health problem in the industrialized world. Recently, the Korean Acute Myocardial Infarction

Registry (KAMIR) study, a nationwide, multicenter study, was initiated to analyze the clinical characteristics of AMI in the Korean population. The current study was designed, based on data obtained from the KAMIR study, to elucidate gender differences among Korean AMI patients.

A gender gap has been suggested to be present in coronary artery disease severity, percutaneous coronary

intervention (PCI) outcomes, and short-term mortality among patients with acute myocardial infarction (AMI).^{2–5} One of the contributing factors to poorer outcomes in women is that women receive reperfusion therapy less often than men, which results in a higher incidence of severe myocardial necrosis.^{6–7} In addition, women have other risk factors that contribute to a poorer outcome.^{6–8} However, some studies have shown similar outcomes between genders after adjustment for other risk factors. One report suggested that the overall mortality is not different between genders, but that the timing and mechanism underlying AMI are different.⁹

The purpose of the present study was to determine and compare in-hospital outcomes after ST-segment elevation myocardial infarction (STEMI) and independent predictors of these outcomes in women and men.

Methods

This study is based on a database collected by the KAMIR National Registry Study. KAMIR is a prospective, multicenter registry study designed to characterize the clinical features and prognosis of AMI in Korean patients. All 41 cardiology centers in Korea were invited to participate in the KAMIR study. At participating sites, consecutive patients admitted with AMI were asked to register to be part of this study. Patients at all centers were eligible for thrombolytic therapy, and PCI was available for all acute STEMI patients. All treatment strategies including reperfusion therapy modality and medications were chosen at the discretion of the attending physicians.

Patients

From November 2005 to July 2007, 4037 consecutive patients were admitted to 41 cardiovascular facilities due to an acute STEMI within 72 hours after symptom onset. All patients were divided into 2 groups according to gender and were compared with regard to baseline clinical characteristics, angiographic findings, treatment modalities, and in-hospital outcomes. Among these patients, 1083 (27%) were women and 2954 (73%) were men.

The study protocol has been reviewed and approved by the institutional review boards of the participating centers.

Data Registry

Detailed data were obtained on patients' demographics, treatment in the emergency room, catheterization findings, and clinical outcome during their hospital stay. Data was collected at each institution; a study coordinator or doctor entered the data into a password-protected, web-based, computerized database program provided by the KAMIR committee. Data coordinators attended meetings at least twice yearly for education; in addition, they reviewed and discussed the study protocol.

Definitions

ST-segment elevation myocardial infarction was diagnosed by a cardiologist in a patient with ≥ 2 of the following criteria: (1) typical chest pain lasting > 30 minutes; (2) development of pathological Q waves or ST-segment and T-wave changes in more than 2 ECG leads; and (3) the typical increase and decrease of serum creatinine kinase levels $2\times$ the upper limit of normal. Hypertension was defined as known hypertension or blood pressure (BP) $\geq 140/90$ mm Hg based on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII guidelines.¹⁰ The diagnosis of diabetes mellitus was based on fasting plasma glucose levels ≥ 126 mg per dL (7.0 mmol per L) or 2-hour postprandial plasma glucose (2 hr PPG) readings ≥ 200 mg per dL (11.1 mmol per L). Metabolic syndrome was defined according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)¹¹ since, cut off values for the definition of obesity in Asian populations have been revised and criteria for metabolic syndrome modified.¹² Metabolic syndrome was diagnosed if 3 or more of the following criteria were satisfied: (1) obesity, defined by a abdominal circumference > 90 cm in men or > 80 cm in women; (2) hypertriglyceridemia if the triglyceride level was ≥ 150 mg/dL; (3) low high-density lipoprotein cholesterol < 40 mg/dL in men or < 50 mg/dL in women; (4) hypertension, defined as known hypertension or a BP $\geq 130/85$ mm Hg; and (5) dysglycemia, defined as known diabetes or a fasting plasma glucose ≥ 110 mg/dL. Dyslipidemia was defined as a fasting total cholesterol concentration of ≥ 200 mg/dL, a fasting triglyceride concentration of ≥ 200 mg/dL, or the use of treatment with medication for dyslipidemia.

In-hospital mortality included death from any cause, cardiac and noncardiac, that occurred before discharge. Cardiogenic shock was defined as a systolic blood pressure < 90 mm Hg for at least 10 minutes with evidence of poor tissue perfusion. Cardiac death was defined as mortality directly related to: (1) cardiogenic shock or congestive heart failure; (2) mechanical complications such as free wall and ventricular septal wall rupture; and (3) sudden arrhythmic death. Noncardiac deaths, such as sepsis and pneumonia, were included in the in-hospital deaths.

Statistical Analysis

Data were expressed as proportions or mean value \pm SD. Differences in categorical variables between the 2 groups were analyzed by the χ^2 test and differences in continuous variables were analyzed by the 2-tailed unpaired *t* test. Multivariate logistic regression analysis was used to determine independent predictors of in-hospital mortality. Statistical significance was defined as a *P* value of $< .05$.

Data were analyzed with the use of SPSS 12.0 for Windows software (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

Differences in demographics, medical history, clinical characteristics, and reperfusion therapy are shown in Table

Table 1. Patient Baseline Characteristics

	Women (n = 1083)	Men (n = 2954)	P Value
Age, years	72.1 ± 9.7	60.7 ± 12.5	<.001
BMI, kg/m ²	23.5 ± 3.6	24.1 ± 3.1	<.001
Metabolic syndrome	751 (69.3%)	1332 (45.1%)	<.001
Previous angina	70 (6.5%)	126 (4.3%)	.004
Previous MI	31 (2.9%)	107 (3.6%)	.239
Previous CABG	3 (0.3%)	15 (0.5%)	.330
Previous PCI	30 (2.8%)	128 (4.3%)	.023
Stroke	80 (7.4%)	159 (5.4%)	.017
Diabetes	333 (31.4%)	667 (23.1%)	<.001
Hypertension	640 (59.7%)	1168 (40.2%)	<.001
Smoking	159 (14.7%)	1738 (58.8%)	<.001
Dyslipidemia	560 (51.7%)	1306 (44.2%)	<.001
MI location			
Anterior	549 (53.6%)	1528 (54.4%)	.911
Inferior	425 (41.5%)	1143 (40.7%)	
Lateral	36 (3.5%)	105 (3.7%)	
Posterior	14 (1.4%)	33 (1.2%)	
Peak CK-MB, ng/mL	1485 ± 1671	2022 ± 2435	<.001
Killip class ≥ II on admission	361 (34.7%)	661 (23.2%)	<.001
Cardiogenic shock on admission	92 (8.5%)	144 (4.9%)	<.001
IABP	63 (5.8%)	127 (4.3%)	.044
LVEF, %	49.77 ± 12.518	50.37 ± 11.923	.192

Abbreviations: BMI = body mass index; CABG = coronary artery bypass graft surgery; IABP = intra-aortic balloon pump; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.

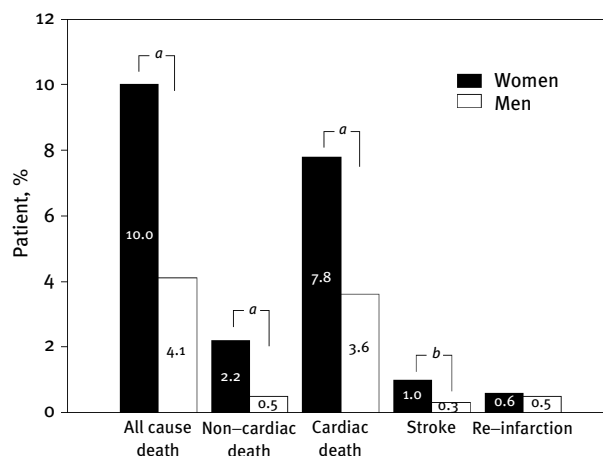


Figure 1. The rates of in-hospital cardiovascular events in women and men. ^a*P* < .001 compared with the men. ^b*P* < .05 compared with the men.

1. Women were significantly older than the men at the time of their AMI (72 ± 10 vs 61 ± 13 years, *P* < .001); more than half of the women patients were older than 70. In addition, women were more likely to have metabolic syndrome, previous angina, stroke, hypertension, diabetes, and dyslipidemia. Among men, there was a higher percentage of smokers and had higher peak creatinine kinase-MB levels. Because of the AMI, women were significantly more likely to have a higher incidence of a Killip class ≥ II and cardiogenic shock on admission.

Revascularization Time and Methods

The percentages of patients who visited the emergency room within 12 hours after chest pain onset or who were treated by reperfusion therapy within 12 hours of symptom onset were higher among men than among women. During their admission, reperfusion or revascularization therapy was performed in 86.3% of women and 90.9% of men (*P* < .001). Men received thrombolytic therapy more frequently than women did. There was no significant difference in the frequencies of primary PCI between women and men (Table 2). There were no significant differences in the proportions of use of medical treatment with glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel, β-blockers, and angiotensin-converting enzyme inhibitors.

Coronary Angiographic Findings

The extent of coronary artery stenosis was more severe in men than in women. The most common infarct-related artery was the left anterior descending coronary artery and there was no difference in its distribution between women and men. After coronary intervention, a thrombolysis in myocardial infarction flow (TIMI) of grade 3 was achieved in 89.4% of women and 93.0% of men (*P* = .001; Table 3).

Table 2. Revascularization Time and Methods

	Women (n = 1083)	Men (n = 2954)	P Value
Chest pain to ER visit < 12 hrs	822 (75.9%)	2404 (81.4%)	<.001
Door to needle time, min	86.51 ± 90.06	74.80 ± 73.59	.230
Door to balloon time, min	177.29 ± 336.31	207.55 ± 652.548	.143
Chest pain to reperfusion Tx < 12 hrs	597 (55.1%)	1866 (63.2%)	<.001
Any reperfusion Tx before discharge	935 (86.3%)	2685 (90.9%)	<.001
Thrombolytic Tx	108 (10.1%)	404 (13.9%)	.002
PCI (%)			
Primary PCI	661 (61.0%)	1873 (63.4%)	.167
Rescue PCI after thrombolysis	38 (3.5%)	113 (3.8%)	.639
Rescue PCI after conservative Tx	31 (2.9%)	76 (2.6%)	.612
Delayed PCI	165 (15.2%)	505 (17.1%)	.159
CABG	20 (1.9%)	38 (1.3%)	.192

Abbreviations: CABG = coronary artery bypass graft surgery; ER = emergency room; PCI = percutaneous coronary intervention; Tx = therapy.

In-Hospital Outcomes

All in-hospital cardiovascular events are summarized in the Figure. During hospitalization, 189 deaths (4.7%) were recorded. The overall mortality rate during hospitalization was 8.6% in women and 3.2% in men ($P < .001$). The frequencies of both cardiac and noncardiac deaths were higher in women than in men ($P < .001$). There were similar frequencies of reinfarction during hospitalization in both men and women. However, a higher proportion of women patients had a stroke during hospitalization (1.2% vs 0.5%, $P = .012$).

Predictors of In-hospital Death

Multivariate stepwise logistic regression models identified the predictors of in-hospital death. Among all patients, age, previous angina, hypertension, a Killip class \geq II, and left ventricular ejection fraction (LVEF) $<40\%$ were identified as independent risk factors. A TIMI flow of grade 3 after coronary intervention was a negative predictor (Table 4).

Discussion

The outcome of AMI in men and women has been the object of debate in numerous studies. In this study, we found different clinical features and higher in-hospital mortality in women compared to men after an AMI. However, after adjustment for confounding factors, female gender was not an independent predictor of in-hospital mortality.

The physiological concentration of female sex hormones is thought to slow the progression of atherosclerosis.¹³

Therefore, gender differences in ischemic heart disease are not appreciated until after the age of 70 in women; this suggests that the antiatherogenic effects associated with female gender decrease and disappear by about 20 years after menopause.¹⁴ Consistent with the findings of other studies, the most striking difference between genders in this study, with regard to the clinical risk profile, was age; women were older by an average of 11 years.^{15,16} Therefore, women had a higher incidence of age-associated risk factors such as diabetes and hypertension. Advanced age in women is commonly associated with many comorbidities in addition to diabetes and hypertension. Thus, for women there was limited use of thrombolytic therapy and invasive procedures.¹⁷

A number of studies have suggested gender differences in morbidity and mortality following an acute myocardial infarction.^{5,8} Although there are a few studies that did not find a gender difference in clinical outcomes,^{16,18} some studies have attributed the gender differences in outcome to less aggressive treatment of women compared to men.⁸ In this study, we found significant gender differences in the incidence of cardiac and noncardiac in-hospital mortality. Explanations for why the female gender was associated with a poorer prognosis are needed. The frequency of hospital visits within the time frame eligible for reperfusion therapy (<12 h after the onset of chest pain) was higher in men than in women. In addition, women tended to present with more serious angiographic and clinical findings, such as cardiogenic shock and a Killip class \geq II than did

Table 3. Coronary Angiographic Findings

	Women (n = 895)	Men (n = 2567)	P Value
Number of diseased vessels			
LMT, complex	12 (1.5)	40 (1.6%)	.004
LMT, isolated	4 (0.5)	9 (0.4%)	
1	370 (41.9)	1230 (48.5%)	
2	278 (31.4)	759 (29.9%)	
3	219 (24.8)	497 (19.6%)	
Infarct-related artery			
LAD	458 (51.8%)	1319 (52.0%)	.281
LCX	75 (8.5%)	258 (10.2%)	
RCA	345 (39.0%)	930 (36.7%)	
LMT	7 (0.8%)	30 (1.2%)	
TIMI flow grade 0 at initial angiography	478 (53.4%)	1324 (51.6%)	.345
Final TIMI flow grade 3	776 (89.4%)	2299 (93.0%)	.001

Abbreviations: LAD = left anterior descending coronary artery; LCX = left circumflex artery; LMT = left main trunk; LMT complex = coronary artery stenosis on left main trunk and other major coronary arteries; RCA = right coronary artery; TIMI = thrombolysis in acute myocardial infarction.

men. The percentages of men with early reperfusion or late revascularization therapy were higher than those in women. The thrombolytic therapy in men accounted for most of this difference. Older patients report chest pain more commonly with atypical symptoms such as nausea, vomiting, dyspnea, and abdominal symptoms.^{19–21} These atypical symptoms may delay a hospital visit in women having an MI and also delay reperfusion therapy. This may cause the resulting gender disparity in hospital arrival time and early treatment. In addition, treatment with proven cardioprotective drugs such as aspirin, heparin, and β -blockers is less common in women.²² Furthermore, thrombolytic therapy, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery are performed less often in women.²²

Does female gender itself increase mortality after an AMI? From the multivariate logistic regression analysis, age, previous angina, hypertension, a Killip class \geq II, an LVEF $<$ 40%, and a TIMI flow \leq grade 3 after angioplasty were identified as independent risk factors for in-hospital death; however, female gender itself was not an independent risk factor. These findings are explained by the observation that highly significant prognostic factors such as Killip

Table 4. Independent Predictors of In-hospital Death in All Patients

Variable	OR (95% CI)	P Value
Age	1.06 (1.027–1.094)	$<$.001
Sex, female	1.36 (0.690–2.660)	.378
Metabolic syndrome	0.99 (0.507–1.935)	.978
Previous angina	2.57 (1.067–6.186)	.035
Stroke	1.04 (0.378–2.840)	.946
Smoking	0.82 (0.402–1.688)	.596
Hypertension	1.96 (1.016–3.792)	.045
Diabetes mellitus	1.41 (0.767–2.609)	.267
Dyslipidemia	0.68 (0.373–1.244)	.211
Killip class \geq II	3.22 (1.779–5.828)	$<$.001
Anterior wall MI	1.03 (0.557–1.893)	.932
LVEF $<$ 40%	3.95 (2.133–7.309)	$<$.001
Reperfusion therapy $<$ 12 hr	0.42 (0.169–1.055)	.065
TIMI flow grade 3 after PCI	0.32 (0.160–0.649)	.002

Abbreviations: CI = confidence interval; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

class, left ventricular function, and TIMI flow of grade 3 after angioplasty were worse in women than in men.

Taken together the results of this study showed that women with an acute STEMI had different risk factors and a higher in-hospital mortality than men. However, female gender itself was not an independent risk factor for in-hospital mortality. Further study is needed to determine the reasons for these gender differences and to develop management protocols to improve patient outcomes.

Appendix

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