Gender differences in in-hospital mortality and mechanisms of death after the first acute myocardial infarction

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BACKGROUND: There are conflicting data about gender differences in short-term mortality after acute myocardial infarction (AMI) after adjusting for age and other prognostic factors. Therefore, we investigated the risk profile, clinical presentation, in-hospital mortality and mechanisms of death in women and men after the first AMI.

METHODS: The data were obtained from a chart review of 3382 consecutive patients, 1184 (35%) women (69.7±10.9 years) and 2198 (65%) men (63.5±11.8 years) with a first AMI. The effect of gender and its interaction with age, risk factors and thrombolytic therapy on overall mortality and mechanisms of death were examined using logistic regression.

RESULTS: Unadjusted in-hospital mortality was higher in women (OR 1.77, 95% CI 1.47-2.15). Adjustment that included both age only and age and other base-line differences (hypertension, diabetes mellitus, hypercholesterolemia, smoking, AMI type, AMI site, mean peak CK value, thrombolytic therapy) decreased the magnitude of the relative risk of women to men but did not eliminate it (OR 1.26, 95% CI 1.03-1.54 and OR 1.31 95% CI 1.03-1.66, respectively). Multivariate analysis revealed that female gender was an independent predictor of in-hospital mortality after the first AMI. Women were dying more often because of mechanical complications—refractory pulmonary edema and cardiogenic shock (P=0.02) or electromechanical dissociation (P=0.03), and men were dying mostly by arrhythmic death, primary ventricular tachycardia/fibrillation (P=0.002). Female gender was independently associated with mechanical death (OR 1.56, 95% CI 1.35-2.58; P=0.01) and anterior AMI was independently associated with arrhythmic death (OR 0.54, 95% CI 0.34-0.86; P=0.01).

CONCLUSION: Our results demonstrate significant differences in mechanisms of in-hospital death after the first AMI in women and men, suggesting the possibility that higher in-hospital mortality in women exists primarily because of the postponing AMI death due to the gender-related differences in susceptibility to cardiac arrhythmias following acute coronary events.

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Accepted for publication
September 2006

Ann Saudi Med 2006;26(6):455-460

Despite major progress in detection, prevention, and treatment, coronary artery disease (CAD) is the leading cause of mortality in males and females. A considerable number of studies have consistently demonstrated that unadjusted short-term mortality after acute myocardial infarction (AMI) is higher in women.[1,2] However, there are conflicting data about gender differences in short-term mortality after AMI, after adjusting for differences in age and other prognostic factors.[2-4]

Some studies indicate that more men with AMI die suddenly before

reaching the hospital, while women with AMI have a worse in-hospital prognosis.[5,6] GUSTO-1 showed that a disproportionate number of men died before hospitalization.[7] Namely, in this study among patients dying during the first 24 hours after symptom onset, men died an average of 1.7 hours earlier than women.[7] More out-hospital deaths in AMI patients are caused by malignant ventricular arrhythmias and more in-hospital AMI deaths are caused by mechanical complications.[1] This suggests possible gender differences in the pathophysiologic mechanism of death after AMI.

Previously we have reported gender differences regarding the type and site of the first AMI, suggesting that the importance of pathophysiological mechanisms for the onset of AMI differs according to gender and age subgroups.[8] The aim of this study was to compare in-hospital outcome in mechanism of death in men and women after the first AMI.

Patients and Methods

We studied 3382 consecutive patients admitted to the coronary care units at the University Hospital Split for a first AMI in the periods from January 1990 until December 1999. For inclusion patients were required to meet two of the following three criteria diagnostic for AMI according to the World Health Organization: (1) typical chest pain that lasted for more than 30 minutes; (2) characteristic ECG changes demonstrating significant evolution such as new pathologic Q-waves or 1-mm ST-segment elevation in any of two or more limb leads or new persistent ST-T wave changes diagnostic of a non-Q-wave AMI; (3) activities of creatine kinase (CK) and/or its isoenzyme CK-MB more than two times the upper limit of normal range.

Trained research assistants abstracted the information from the hospital medical record and entered the data into an electronic database. The data included demographic variables, prior cardiac history, clinical course during hospitalization, laboratory data and ECG. The clinical variables analyzed were age, gender, hypertension, hypercholesterolemia, diabetes, cigarette smoking, type and site of AMI, peak CK level, thrombolytic therapy and hemodynamic condition, estimated according to the Killip classification (Killip class I-IV).

AMI was classified as Q-wave or non-Q-wave (based on review of all hospital ECGs) if ST-segment and T-wave abnormalities were observed with or without progression to pathologic Q waves. With regard to ECG location, all AMI were classified as anterior (septal, anterolateral, high lateral, extensive location—an alteration in one or more of the following lead groups: V1-V3; V4-V6; D1 and AVL) or inferior (inferior, inferolateral, inferodorsal, laterodorsal, inferolaterodorsal location—an alteration in one or more of the following lead groups: D2, D3, AVF; D1, AVL; V5 and V6; V7 and V8). In the group of undetermined type and site of AMI there were 424 patients (12% of all patients) with left bundle branch block, right ventricular stimulation, complete heart block with wide QRS, preexcitation or unspecific EKG changes.

Arterial hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication. Hypercholesterolemia was defined as a total serum cholesterol level >5 mmol/L or the use of lipid-lowering therapy. Diabetes was defined as a fasting plasma glucose level >6.9 mmol/L or a non-fasting plasma glucose level ≥11.0 mmol/L, and/or the use of antidiabetic medication. Smoking was categorized as no smoking or smoking (current or stopped <1 year ago).

Cardiac deaths were grouped into three categories:

Arrhythmic death. Death from rapid ventricular tachycardia (VT), ventricular fibrillation (VF) or asystole (AS); the loss of cardiac output and pulse was sudden and preceded collapse of the circulation (defined as a state of very low cardiac output, poor peripheral perfusion, systolic blood pressure <80 mm Hg, or dependence on intravenous inotropic support) or severe pulmonary edema, characterized by severe respiratory distress of a sudden onset without evidence of non-cardiac cause. The patient was not in shock or pulmonary edema at the time of the onset of the arrhythmia.

Mechanical death. A collapse of the circulation or cardiogenic shock or severe pulmonary edema before the loss of cardiac output and fatal arrhythmia. Special categories included monitored patients who had a rhythm generally compatible with the normal cardiac output and, therefore, probably electromechanical dissociation, immediately before an abrupt circulatory collapse (electromechanical dissociation is the most common manifestation of the left ventricular rupture).[9,10]

Unwitnessed presumed cardiac death. Sudden cardiac deaths in non-monitored patients were presumed to be cardiac if there were no alternative diagnosis, such as aortic dissection, ruptured aneurysm, cerebral vascular accident, or pulmonary embolus.

We compared the base-line characteristics and clinical outcomes of women with those of men. Continuous variables were presented as mean value±standard deviation, and dichotomous variables as the percentage of presence in a particular subgroup. Group differences in continuous variables were compared by two tailed t-test and Mann-Whitney U test. Dichotomous variables were compared by the chi-square test with Yates' con-

tinuity correction or Fishers' exact test. To determine whether the differences in mortality between men and women were due to differences between the genders in the baseline clinical and demographic characteristics, we adjusted for these variables by logistic regression models. First, a possible interaction between gender and age was tested using logistic regression with an interaction term (age × sex) created with age as a continuous variable. After that, in order to determine independent predictors of AMI death mechanism, a logistic regression was performed, in which we entered variables with a *P* value <0.20 in the univariate analysis. Those variables were age, risk factors (hypertension, diabetes, hypercholesterolemia, smoking), the type of AMI, site of AMI, hemodynamic condition (Killip class I-IV) and thrombolytic therapy. Results are expressed as odds ratio (OR) estimates, 95% confidence interval (CI) and a *P* value. Statistical significance was defined as $P<0.05$. All statistical analyses were performed with the SPSS statistical software package (version 8.0, Statistical Package for the Social Sciences Inc., Chicago, USA).

Results

Baseline clinical data on the 3382 patients are presented in Table 1. Women were older than men, had greater comorbidity and were more hemodynamically compromised. Specifically, women more often had hypertension, diabetes, hypercholesterolemia, but were less commonly cigarette smokers than men. Significantly, more women presented with non-Q-wave AMI and were in higher Killip classes (Killip III and IV). Mean adjusted CK levels were higher in men than in women. Systolic and diastolic blood pressure at admission, and frequency of AMI site did not differ significantly between the genders. Five-hundred-thirty-six (15.8%) patients received thrombolytic therapy. All the patients received streptokinase. Thrombolysis was applied less frequently in women than in men. In both genders the use of thrombolytic therapy declined with age.

The overall in-hospital mortality was higher among women than among men. In both genders mortality rate increased with age. After we compared the mortality rate among women and men according to three age groups (<45 years, 45 to 64 years, ≥65 years), we found higher mortality in women than in men only in patients ≥65 years (Table 2). Crude comparisons of mortality among women and men in broad age groups suggested that much of the difference in mortality reflected differences in age distribution between the women and men. To identify whether female gender was an independent predictor of in-hospital mortality a logistic regression was performed. Adjustments that included both age

Table 1. Characteristics of the study population.

	Women	Men	*P* value
Patients in cohort	1184 (35)	2198 (65)	
Age (yrs, mean ± SD)	69.7±10.9	63.5±11.8	<0.001
Hypertension	592 (50)	879 (40)	<0.001
Diabetes	367 (31)	396 (18)	<0.001
Hypercholesterolemia	391 (33)	593 (27)	<0.001
Cigarette smoking	166 (14)	791 (36)	<0.001
AMI site			0.59
Anterior	504 (42.6)	981 (44.5)	
Inferior	514 (43.4)	959 (43.5)	
Undetermined	166 (14)	258 (12)	
AMI type			<0.001
Q-wave	703 (59)	1485 (67)	
Non-Q-wave	315 (27)	455 (21)	
Undetermined	166 (14)	258 (12)	
Mean peak creatine kinase level (IU)	823.6±810.2	997.8±939.7	<0.001
Killip class			<0.001
Killip I (no heart failure)	911 (77)	1802 (82)	
Killip II (heart failure)	143 (12)	286 (13)	
Killip III (pulmonary oedema)	71 (6)	66 (3)	
Killip IV (cardiogenic shock)	59 (5)	44 (2)	
Thrombolytic therapy	110 (10)	370 (19)	<0.001
< 45 years	6 (29)	50 (40)	0.6
45-64 years	40 (16)	166 (20)	0.25
> 65 years	64 (8)	154 (16)	0.002

Values are number (%) of patients unless otherwise noted.

Table 2. In-hospital mortality after the first AMI by gender and age.

	Women 1184 (35)	Men 2198 (65)	*P* value*
Total	272 (23)	284 (14)	<0.001
< 45 y	0 (0)	2 (0.1)	0.58
45-64 y	34 (2.9)	83 (3.8)	0.13
≥ 65 y	239 (20.2)	228 (10.4)	0.002
P value**	0.001	<0.001	

Values are number (%) of patients statistical comparisons: * Women vs. men; **Between age categories

Table 3. Female gender as a predictor of in-hospital mortality after the first AMI before and after adjustment for age and other covariates.

	OR (95% CI)	*P* value
Unadjusted	1.77 (1.47 - 2.15)	<0.0001
Adjusted for age	1.31 (1.03 - 1.66)	0.02
Adjusted for age and other covariates*	1.26 (1.03 - 1.54)	0.03

*Other covariates: AMI type and site, peak CK level, Killip classes, thrombolytic therapy

Table 4. Causes of in-hospital mortality for men and women.

	Women 272 (23)	Men 308 (14)	*P* value
Arrhythmic death			
Asystole	35 (13)	46 (15)	0.46
Ventricular tachycardia or fibrillation	33 (12)	68 (22)	0.002
Mechanical death			
Pulmonary edema + cardiogenic shock	101 (37)	83 (27)	0.02
Electromechanical dissociation	60 (22)	37 (12)	0.03
Unwitnessed death	43 (16)	68 (22)	0.12

Values are number (%) of patients.

Table 5. Predictors of in-hospital death.

	Univariate analysis	
Arrhythmic vs. mechanical	**OR (95% CI)**	***P* value**
Female gender	1.64 (1.40–2.90)	0.01
Q AMI	1.21 (0.74–1.97)	0.002
Hypercholesterolemia	0.80 (0.46–1.42)	0.0001
Anterior AMI	0.75 (0.50–1.12)	0.17
Age	1.00 (0.98–1.02)	0.53
Hypertension	0.98 (0.65–1.49)	0.95
Creatinine kinase value	1.00 (0.99–1.00)	0.73
Smoking	0.85 (0.45–1.61)	0.63
Diabetes mellitus	0.72 (0.41–1.25)	0.24
	Multivariate analysis	
Female gender	1.56 (1.35–2.58)	0.01
Anterior AMI	0.54 (0.34–0.86)	0.01

only and age and other baseline differences (hypertension, diabetes mellitus, hypercholesterolemia, smoking, AMI type, AMI site, mean peak CK value, thrombolytic therapy) decreased but did not eliminate the magnitude of the relative risk in women compared with men (Table 3). Therefore, logistic regression revealed that female gender was an independent predictor of in-hospital mortality after the first AMI.

Women died more often because of mechanical complications (refractory pulmonary edema and cardiogenic shock or electromechanical dissociation), and men died mostly by arrhythmic death, especially because of ventricular tachycardia and fibrillation (Table 4). Logistic regression revealed female gender as independent predictor of mechanical death and anterior AMI as an independent predictor of arrhythmic death (Table 5).

Discussion

The main finding of our study was that mechanisms of in-hospital death after the first AMI were different in women and men. Specifically, women died more often because of mechanical AMI complications, whereas men died more often due to arrhythmic death. Some previous reports have demonstrated that, in comparison to men, more women suffering AMI outside the hospital survived to admission.[5-7] However, admitted women experienced a more severe first AMI than their male counterparts.[1,3,11,12] As an overall result, there was no statistically significant difference between the genders in total case-fatality rates to discharge.[11] This suggests that the initial advantage experienced by women represents a postponing of death rather than avoidance.[7] It is well known that in most out-hospital AMI deaths the presenting rhythm is VF or pulseless VT. Therefore, it is possible that gender differences in mechanisms of death that were confirmed in our study contribute to gender differences in in-hospital mortality after AMI.

When in-hospital mortality rates were adjusted simultaneously for differences in age, personal and medical histories and initial clinical findings, we found that female gender was an independent predictor of in-hospital mortality after the first AMI, a finding consistent with some previous reports.[1,2] On the other hand, some authors suggest that although women have higher in-hospital mortality than men, female gender itself is not independently associated with increased in-hospital mortality after adjustment for baseline differences.[3,11,12] Since differences between men and women in risk of death were independent of baseline variables, it is possible that other factors are likely to influence the prognosis. For example, gender-related differences in thrombotic and fibrinolytic activity, extent and severity

of CAD, or differences in susceptibility to cardiac arrhythmias may influence the outcome of patients after the first AMI. While similar mechanisms operate to induce CAD in both genders, some have speculated that sex hormones modify the course of disease causing differences in the dynamics of atherogenesis and the importance of pathophysiological processes that are involved in AMI development in women and men.[8,13] Also, gender-related differences in development of arrhythmias following acute coronary events have been reported.[14]

The abrupt rupture of a vulnerable plaque, resulting in thrombotic occlusion of a coronary artery, is a common cause of sudden death in the AMI population. Extensive studies in experimental animals and increasing clinical evidence indicate that autonomic nervous activity has a significant role in modifying the clinical outcome. Sympathetic hyperactivity supports the genesis of life-threatening ventricular tachyarrhythmias, while vagal activation exerts antifibrillatory effects.[15] It has been demonstrated that vagal activation is more common in women than in men during abrupt coronary occlusion and may have beneficial antiarrhythmic effects, modifying the outcome of acute coronary events.[14] Furthermore, it has been reported that women have a longer corrected QT interval and lower QT dispersion, which may reflect differences in repolarisation.[16] Possible reasons include a direct effect of estrogen and progesterone, or differences in autonomic innervations. Although the prolonged QT interval and QT dispersion are both associated with AMI, it has previously been reported that QT dispersion, rather than the QT interval duration, could be more predictive for ventricular arrhythmias in AMI.[17] Therefore, gender differences in autonomic regulation and differences in susceptibility to cardiac arrhythmias may afford women some protection against the development of arrhythmias following acute coronary events.[14] Those findings may also explain the observation that more men die because of malignant ventricular arrhythmias and more women die because of mechanical AMI complications.

Our study also corroborates that the prevalence of congestive heart failure and cardiogenic shock after AMI is higher in women than in men,[3,18-20] even though left ventricular ejection fraction is equal or higher in women, and there are no gender differences in the frequency of anterior AMI and the AMI size. This apparent paradox may be attributed to the more frequent presence of diastolic dysfunction in women than in men. It has been shown that gender-related differences in cardiac remodeling in ischemic cardiomyopathy are largely related to fundamental differences in cellular remodeling rather than simply differences in infarct size.[21,22] Those findings support the hypothesis that gender-based differences in myocardial biology contribute to gender differences in clinical outcomes and therapeutic responses following AMI.

Earlier studies have shown that because of the relative paucity of advanced coronary stenoses before their infarction, women may not have previously generated an ischemic response capable of protecting the myocardium during an infarction by triggering preconditioning, and/or the development of a collateral blood supply.[23,24] On the other hand, a protracted course of subclinical CAD accompanied by repeated periods of ischemia in men stimulates the development of a collateral circulation.[22-25] Therefore, coronary artery occlusion and insufficient collateral blood supply in women may result in smaller, clearly differentiated transmural infarctions that could be the most frequent cause of electromechanical dissociation because of a thinner ventricle, and more commonly, arterial hypertension in women (frequently accompanied with left ventricular free wall rupture).[9,10] Supporting this possibility, Murphy et al previously reported that in females culprit lesions were more often distal to the second segment of the culprit artery, possibly reflecting a smaller area at risk.[26]

Despite the evidence that thrombolysis performed during the first few hours after AMI onset decreases the infarct size, improves left ventricular function, and reduces mortality, pharmacoepidemiologic data seem to indicate underutilization of thrombolytic treatment.[27] Because of admission delays, presenting ECG with ST depression only, and absolute or relative contraindications to thrombolysis, the optimal rate of administration in patients admitted to coronary care units with an AMI is estimated to be 55% to 60%.[27] Recently, Khalil and Abba reported that 80.9% of AMI patients admitted to the Coronary Care Unit of Riyadh Medical Complex received thrombolytic therapy.[28] Unfortunately, our results, as well as some prior reports,[29,30] demonstrated that in Croatian hospitals less than 30% of AMI patients received thrombolysis. The admission delay is the main reason for no application of thrombolysis in Croatia. Contrary to the experience from Saudi Arabia that the median pain-to-needle time is around 5 hours,[31] in our country that time is 7 hours or more.[29]

It has also been previously reported that women and the elderly have been undertreated because of a higher risk of complications of thrombolytic therapy.[30,32,33] Heer and colleagues reported that the percentage of patients who were eligible for thrombolysis and received no reperfusion was higher in women than in men.[4]

Therefore, the less frequent use of thrombolysis in women than in men in our study corresponds with prior reports.[4,32,33] Less frequent use can also be explained by the greater age and comorbidity in women, which increases the risk of potential treatment complications, in particular free wall rupture and intracranial hemorrhage.[30,34] An additional factor explaining less frequent use of thrombolytic therapy may be the less severe or atypical AMI presentation in women, resulting in their delayed hospitalization.[35] Less frequent administration of thrombolytic therapy could be responsible for the higher mortality among women in our study. However, a multivariate analysis revealed female gender as an independent predictor of in-hospital AMI death.

Our study has several limitations. First, only in-hospital patient outcomes were analyzed, so we could not test the hypothesis that men die more frequently before they arrive at the hospital. Second, our data set did not include information about the treatment of patients with aspirin, beta-blockers and ACE inhibitors, all of which have been proved to reduce mortality related to AMI. Third, the mechanisms of death were assessed only on the bases of clinical and ECG data.

In conclusion, the present study demonstrates significant differences in mechanisms of in-hospital death after the first AMI in women and men. Therefore, it is possible that higher in-hospital mortality in women primarily exists because of postponing the AMI death due to the gender-related differences in susceptibility to cardiac arrhythmias following acute coronary events.

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