

# Sex Differences in Mortality After Myocardial Infarction

## Evidence for a Sex-Age Interaction

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**Background:** Studies of sex differences in mortality after myocardial infarction (MI) have shown conflicting results.

**Objectives:** To test the hypothesis that sex differences in mortality after MI vary according to patients' age, with younger women, but not older women, having a higher mortality compared with men.

**Methods:** We performed a retrospective cohort study of 1025 consecutive patients who met accepted criteria for MI in 1992 and 1993 in 15 Connecticut hospitals. Data for the study were abstracted from medical records.

**Results:** Women had a 40% higher hospital mortality rate than men. Simple age adjustment eliminated the sex difference in mortality rate (odds ratio, 0.99; 95% confidence interval, 0.66-1.48). However, when the sample was subdivided into 2 age groups, women

younger than 75 years showed twice as high a mortality rate as men in the same age group, while among older patients no difference in mortality was found. In multivariate analyses the interaction of sex with age was highly significant, even after adjusting for comorbid conditions, clinical severity, process of care, and hospital characteristics. In the fully adjusted model, this interaction indicated that among patients younger than 75 years women had 49% higher odds of hospital death than men, while in the age group 75 years or older women had 46% lower odds of death compared with men.

**Conclusions:** A higher mortality of women compared with men after MI is confined to the younger age groups. The sex-age interaction should be considered when examining sex differences in mortality after MI.

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**S**TUDIES OF sex differences in mortality after myocardial infarction (MI) have consistently indicated that women have higher unadjusted mortality rates, especially for short-term follow-ups (hospitalization or first month).<sup>1</sup> However, data are conflicting regarding whether mortality remains higher in women after adjusting for differences in age and other prognostic factors. While in a number of studies<sup>2-11</sup> such adjustment resulted in a similar outcome in men and women, in other studies<sup>12-18</sup> it failed to account for the higher mortality rates of women.

Differences in the age distribution of study samples may explain some of the discrepancies of findings across studies. Studies of elderly populations with MI have consistently found either no significant differences in mortality between men and women,<sup>19,20</sup> or even a lower mortality rate among women.<sup>21,22</sup> In contrast, hospital series that have excluded elderly subjects have often found higher mortality rates among

women.<sup>13,17</sup> Furthermore, studies<sup>23-25</sup> that have analyzed separately the mortality experience of younger and older patients have usually shown that the worse prognosis of women was confined to the younger age groups.

These previous data suggest that the association of sex with mortality depends on the patients' age, and that much of the difference in outcome of MI between men and women described in previous literature may be due to sex differences at younger ages. However, the finding that the relationship of sex with mortality varies according to age has usually been incidental and somewhat unappreciated in previous literature. Consequently, little has been done to better describe and understand these results. Presumably age-related sex differences in comorbidity and process of care are 2 key explanatory factors for the age-dependent effect of sex on post-MI mortality. Some of the previous studies<sup>24</sup> were based on administrative data sets in which comorbidity information was likely to be incomplete. On

## METHODS

### STUDY SAMPLE

This study is based on the Myocardial Infarction Project II, a database developed for quality improvement purposes by the Connecticut Peer Review Organization and 15 Connecticut hospitals. The details of this project have been published earlier.<sup>26</sup> Participating hospitals ranged from 92 to 875 beds and included both teaching and nonteaching institutions. All had intensive care units. Two thirds of these hospitals had catheterization facilities, while one third also had revascularization facilities.

Patients included in the database were those who were hospitalized in these 15 institutions in 1992 and 1993 and had a principal discharge diagnosis of acute MI (*International Classification of Diseases, Ninth Revision, Clinical Modification*,<sup>27</sup> code 410). Cases were selected from hospital discharge records beginning in December 1993 and working backward consecutively until at least 50 cases were assembled from each hospital. Trained nurses and medical record technicians abstracted the medical records of these patients to obtain information on demographics, medical history, clinical characteristics on admission, treatments, and hospital mortality. If patients were discharged to another acute care facility, medical charts of the second hospitalization were also reviewed to assess process of care and outcomes. The database also contained information on hospital characteristics, ie, number of beds and cardiovascular services offered. The hospitals were classified as offering (1) full invasive cardiovascular services, ie, coronary angiography, angioplasty, and bypass surgery; (2) partial invasive cardiovascular services, ie, only coronary angiography; or (3) no invasive cardiovascular services. Each of these cardiovascular peer groups included 5 hospitals.

Patients were included in the present study if they had a peak creatine kinase (CK) MB fraction of more than 5% of total CK, or at least 2 of the following criteria: presence of chest pain on admission; ST-segment elevation consistent with acute MI in at least 2 contiguous leads; and a 2-fold elevation of the CK level. However, when only one CK value was available, this was considered to fulfill enzyme

criteria if it was above the normal limit (to avoid the potential bias that patients might have died before a peak CK value was obtained).

### STUDY VARIABLES

In most analyses, patients were classified into 1 of 2 age groups according to whether they were younger than 75 years or 75 years or older. This age cutoff point, which was slightly greater than the median age (71 years), was chosen because of few women in the younger age groups. In addition, 75 years represents the age up to which the rate of MI is lower in women compared with men,<sup>28</sup> and up to which genetic components to coronary heart disease incidence in women are particularly strong.<sup>29</sup> Therefore, this age cutoff point allowed us to define a group of female patients with premature MI who may have a particularly aggressive coronary atherosclerosis or other predisposing factors to more severe coronary heart disease outcomes.

Historical and clinical characteristics that were available for analysis included history of congestive heart failure, history of stroke, history of diabetes treated with insulin, history of severe hypertension (defined as history of uncontrolled hypertension, admission systolic blood pressure  $\geq 200$  mm Hg, or diastolic blood pressure  $\geq 120$  mm Hg), renal insufficiency (defined as an admission laboratory value of creatinine  $> 176.8$   $\mu\text{mol/L}$  [ $> 2$  mg/dL]), anemia (admission hematocrit,  $< 0.3$  or hemoglobin,  $< 0.01$  g/L), location of the infarction (anterior vs other locations), Killip class,<sup>30</sup> and first creatine kinase level greater than 3 times the upper normal limit. The Killip classification is based on 4 categories: 1, no heart failure, ie, absence of any sign of cardiac decompensation; 2, heart failure; 3, pulmonary edema; and 4, cardiogenic shock. Process of care variables included treatments and features on admission or within 24 hours from admission: use of thrombolytics, aspirin,  $\beta$ -blockers, or angiotensin-converting enzyme inhibitors within 24 hours from hospital arrival, and presence of a cardiologist as admitting or attending physician. We deliberately chose to include in the analysis only those treatments recommended on admission or in the first 24 hours<sup>31</sup> to minimize a bias due to early mortality, ie,

Continued on next page

the other hand, treatment differences have never been considered as a potential explanation for outcome differences between women and men in different age groups.

The purpose of this study was therefore to assess whether sex differences in mortality after MI depend on the patients' age, irrespective of differences in comorbidity and treatment factors. Our specific hypothesis was that in younger age groups women tend to have a worse prognosis than men, while in older age groups there are no differences in prognosis or even the inverse may be true.

## RESULTS

### STUDY SAMPLE AND BIVARIATE ANALYSES

The Myocardial Infarction Project II database included 1212 patients. Of these, 97 patients (45 men and 52 women) were excluded because they did not meet criteria for

MI. An additional 80 patients (49 men and 31 women) were excluded because outcome in transfer hospitals was unknown. Finally, 10 patients (5 men and 5 women) were eliminated because of missing information on baseline clinical variables. Therefore, 1025 patients, 594 men and 431 women, were left for analysis. Of these patients, 211 (137 men and 74 women) were transferred to other acute care facilities, and therefore had the primary and transfer hospitalization linked to assess outcome.

**Table 1** shows comparisons of baseline characteristics between women and men after stratification by age. In both age groups women were significantly older than men. In the age group younger than 75 years, women had more comorbid conditions than men: they were more likely to report a history of congestive heart failure, diabetes treated with insulin, and stroke, as well as to have renal insufficiency and anemia on admission. In contrast, fewer sex differences in comorbid conditions were

patients may die before such treatments are initiated. For the same reason we did not consider cardiac procedures such as catheterization and revascularization, since these usually occurred at different time points after the first hospital day. In addition to use of thrombolytic therapy in the first 24 hours, we examined sex differences in length of time from admission to administration of thrombolytic therapy in the first 24 hours. We also examined sex differences in time from onset of symptoms to hospital arrival, but this information was limited to a subset of patients who reported chest pain and for whom the time of onset of chest pain was documented. Hospital characteristics considered in the analysis included hospital size greater or less than the median hospital size (350 beds), presence of coronary angiography, and presence of coronary revascularization facilities (peer group).

#### STUDY OUTCOME

The end point of this study was hospital mortality rates. For those patients who were transferred to another acute care facility, the outcome in the transfer hospital was included in the outcome measure.

#### STATISTICAL ANALYSIS

The purpose of the statistical analysis was to test whether the mortality experience of women compared with men during hospitalization differed according to age (ie, whether there was a significant sex-age interaction with mortality), after adjusting for differences in comorbidity and other risk factors.

First, we performed bivariate comparisons of baseline characteristics between women and men after stratification according to the 2 age groups. Statistical significance of bivariate associations was tested by using the  $\chi^2$  statistic for dichotomous variables and the Student *t* test for continuous and normally distributed variables.

Next, we sought to test whether there was a significant interaction between sex and age for hospital mortality and whether such interaction would be still significantly associated with mortality after adjusting for a number of baseline differences between men and women. We con-

structed a series of hierarchical logistic regression models in sequential fashion. The first model included sex as the sole explanatory variable. The second model included sex and age. In the third model, the interaction term of sex with age was added to the previous factors. This interaction term tested the hypothesis that the association between sex and mortality differs according to age group, younger than 75 years or 75 years or older, and allowed the calculation of odds ratios (ORs) of mortality for women vs men within each age group, before adjusting for differences in risk factors between sexes, except age. In subsequent models, the following characteristics were added: comorbid conditions, clinical severity on admission, process of care on admission or in first 24 hours, and hospital characteristics. This method of hierarchical modeling allowed us to assess the impact of each of the features sequentially added to the model on the association between sex and mortality in each of the 2 age groups.

To be reassured that the results were not dependent on the age cutoff point chosen, we repeated the analyses using sex-age interactions that treated age in different ways, ie, age as an ordinal variable according to deciles, age as a continuous variable, and age categorized into 4 age groups. Aside from the interaction term, age in the models was treated as a continuous factor, since no significant departure from linear trend for age was found. In this way, we ensured that any residual age difference between women and men within each of the 2 groups under study, ie, younger than 75 years and 75 years or older, would be taken into account.

To allow comparisons of estimates among sequential models, once included, factors were not allowed to drop out of the models. Model reduction was only performed after the final model was fitted by using a backward elimination procedure with exit significance level of .05. Sex, age, and the interaction of sex with age were forced in this model. The model was also repeated without forcing the interaction. Adequacy of model fit was assessed in all these models by inspecting residual plots and influence statistics,<sup>32</sup> as well as by goodness-of-fit test, which compared observed and expected responses within deciles of outcome probability.<sup>33</sup> Interactions of sex with other variables were also tested in all the models.

found in the older age group. In both age brackets women and men showed remarkably similar clinical characteristics on admission, including Killip class and creatine kinase levels more than 3 times the upper normal limit. However, there were differences in the location of the infarction, anterior infarction being more common in older women compared with older men. In the younger age group women tended to receive thrombolytic therapy, aspirin, and  $\beta$ -blockers in the first 24 hours less often than men, and women were less likely to receive care from a cardiologist on admission. In the older age group only a lower use of aspirin in women with respect to men was noted. Sex differences in time from onset of symptoms to hospital presentation were not found, although these data were available only among those patients (396 men and 260 women) who reported chest pain and had a time onset documented. The time from admission to thrombolytic therapy among patients who received thrombo-

lytic therapy within 24 hours was also similar in the 2 sexes in both age groups. There were also no differences between women and men in the characteristics of the hospitals where they were admitted (peer group or hospital size). Despite the similarities in admission characteristics, length of hospital stay was on average 2 days longer in younger women (9 days) than in younger men (7.4 days), while it was similar in the older women and men.

In the whole sample women had a 40% higher hospital death rate than men (14.4% vs 10.3%). However, when mortality was examined by age group, women younger than 75 years had a hospital mortality rate that was almost twice as high as men in the same age group, while no difference in mortality was found among older patients (Table 1). To assess whether similar sex differences in mortality would be found using a finer age breakdown, we calculated mortality rates by age decile in women and men. **Figure 1** shows that women had a

**Table 1. Demographic and Clinical Characteristics in Women and Men According to Age Group\***

	Age <75 y			Age ≥75 y		
	Women (n = 208)	Men (n = 417)	P	Women (n = 223)	Men (n = 177)	P
Mean (SD) age, y	63.5 (8.5)	60.4 (10.5)	<.001	82.7 (5.7)	80.6 (4.4)	<.001
History of congestive heart failure	44 (21.2)	62 (14.9)	.05	103 (46.2)	71 (40.1)	.22
Insulin therapy	50 (24.0)	42 (10.1)	<.001	34 (15.3)	15 (8.5)	.04
History of stroke	23 (11.1)	19 (4.6)	.002	35 (15.7)	21 (11.9)	.27
Severe hypertension†	11 (5.3)	26 (6.2)	.64	17 (7.6)	11 (6.2)	.58
Renal insufficiency on admission‡	16 (7.7)	11 (2.6)	.003	13 (5.8)	14 (7.9)	.41
Anemia on admission§	12 (5.8)	6 (1.4)	.002	11 (4.9)	9 (5.1)	.95
Anterior infarction	49 (23.6)	98 (23.5)	.99	64 (28.7)	32 (18.1)	.01
Killip class III or IV	21 (10.1)	43 (10.3)	.93	53 (23.8)	44 (24.9)	.80
First creatine kinase level >3 times the normal limit	28 (13.5)	59 (14.2)	.80	20 (9.0)	20 (11.3)	.44
Thrombolytic therapy in first 24 h	70 (33.7)	171 (41.0)	.08	36 (16.1)	33 (18.6)	.51
Mean (SD) time (hours) from admission to thrombolytic therapy in first 24 h	1.9 (3.3)	1.5 (2.3)	.36	2.2 (4.1)	2.0 (3.8)	.82
Mean (SD) time (hours) from onset of chest pain to hospital arrival	5.5 (8.3)	5.0 (7.8)	.54	4.8 (5.0)	4.5 (7.2)	.68
Aspirin in first 24 h	166 (79.8)	353 (84.7)	.13	147 (65.9)	138 (78.0)	.008
β-Blockers in first 24 h	84 (40.4)	204 (48.9)	.04	79 (35.4)	59 (33.3)	.66
Angiotensin-converting enzyme inhibitors in first 24 h	23 (11.1)	44 (10.6)	.85	53 (23.8)	39 (22.0)	.68
Cardiologist on admission or as attending physician	102 (49.0)	244 (58.5)	.02	87 (39.0)	80 (45.2)	.21
Hospital peer group						
Catheterization and revascularization	63 (30.3)	141 (33.8)	.61	90 (40.4)	57 (32.2)	.06
Catheterization only	80 (38.5)	146 (35.0)		57 (25.6)	64 (36.2)	
Neither	65 (31.3)	130 (31.2)		76 (34.1)	56 (31.6)	
Hospital size (≥350 beds)	86 (41.4)	186 (44.6)	.44	110 (49.3)	79 (44.6)	.35
Mean (SD) length of hospital stay, d	9.0 (6.9)	7.4 (4.8)	.002	10.0 (7.8)	9.3 (7.4)	.31
In-hospital death	23 (11.1)	27 (6.5)	.05	39 (17.5)	34 (19.2)	.66

\* Values are number (percentage) unless otherwise indicated.

† History of uncontrolled hypertension or systolic blood pressure of 200 mm Hg or higher or diastolic blood pressure of 120 mm Hg or higher on admission.

‡ Admission creatinine level of more than 176.8 μmol/L (>2 mg/dL).

§ Admission hematocrit of less than 0.3 or admission hemoglobin of less than 0.01 g/L.

|| Two hundred sixty women and 396 men.

higher mortality rate than men in the 2 younger age groups, while in the older age groups either there was no sex difference in mortality, or men had higher mortality rates.

### MULTIVARIATE ANALYSES

The first part of our multivariate analyses addressed the main effect of age on the relationship between sex and hospital mortality. When sex was the only variable in the model, women showed almost 50% higher odds of hospital mortality compared with men (OR, 1.46; 95% confidence interval [CI], 1.01-2.14). However, age adjustment appeared to explain completely the sex difference in mortality (OR, 0.99; 95% CI, 0.66-1.48).

The second part of the analysis assessed the role of the sex-age interaction and provided estimates of the association between sex and mortality separately in the 2 age groups, ie, younger than 75 years and 75 years or older, before and after adjusting sequentially for a number of risk factors for mortality (Table 2). The sex-age interaction was added to the model that included age and sex and was found to be statistically significant (P = .01). Odds ratios calculated from this model indicated that the odds of mortality were almost 70% higher in women compared with men in the age group younger than 75 years, while the odds of mortality were about 30% lower among

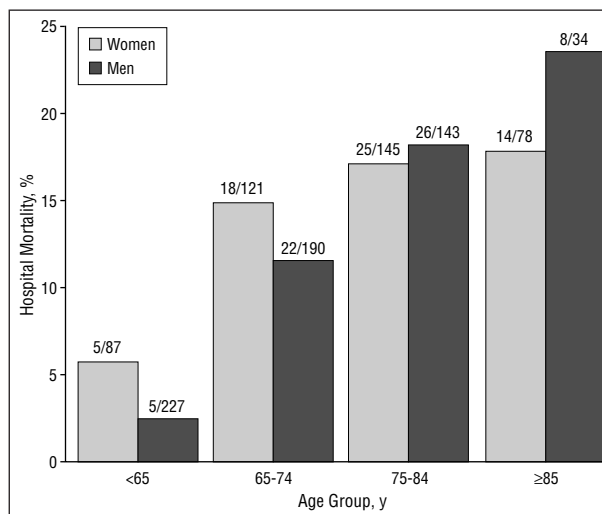


Figure 1. The in-hospital mortality of women and men by age group.

women 75 years or older. Adjustment for comorbidity had some impact in the younger age group but not in the older age group. This result was expected given that there were substantial differences in comorbidity between men and women among patients younger than 75 years, but not among older patients. Additional adjustment for clinical severity variables, process of care, and hospital char-

acteristics further reduced the odds of mortality of women compared with men in the younger age group. However, in this model (step 4 in Table 2), women had still almost 50% higher odds of hospital death than men if they were younger than 75 years. On the other hand, the same model showed that women had almost 50% lower odds of death compared with men if they were 75 years or older after adjustment for all the factors mentioned earlier. Although within each age group sex differences in mortality did not usually reach statistical significance (as shown by the CIs that in most models include 1), the significant interaction indicates that across the 2 age groups the mortality experience of women differed significantly compared with men. The fact that the CIs for the 2 age groups overlap is not in contradiction with the significant interaction. In fact, the 95% probability for the CIs in Table 2 is computed for the ORs in the 2 separate age strata, while an appropriate test for equality of the 2 ORs would have to consider the 2 ORs simultaneously. Therefore, while these CIs are analogous of tests of statistical significance for the effect of sex within age group, they should not be used to test whether the effect of sex differs in the 2 age groups.

When we used different scales of measurement for age (age ordinal according to deciles, age categorical according to 4 age groups, and age continuous), the results indicated that the younger the age group, the worse the outcome of women compared with men.

**Figure 2** illustrates further the results of the multivariate analysis. Adjusted death rates were calculated from the most complete model (step 4 in Table 2) using an ordinal measure of age in the interaction term and plotted against age separately for women and men. The graph clearly illustrates the interaction effect of sex and age on mortality. Women at younger ages have higher death rates than men, but because their death rates increase less

steadily with age than in men, at older ages men have higher rates.

## COMMENT

This study introduces a novel way of thinking regarding the controversy over whether outcome after MI differs between women and men. Simple age adjustment appeared to eliminate the higher mortality of women compared with men. This result is consistent with several previous studies<sup>1</sup> that have found that the older age of the women is the major explanatory factor for their higher death rates after MI. However, when the mortality experience of women and men was compared within age strata by examining the interaction of sex with age, our findings indicated that there is a marked difference in outcome after MI of women compared with men depending on age. Women younger than 75 years showed a higher mortality rate than men, but among patients aged 75 years or older the inverse appeared to be true. In addition, the younger the age group, the worse the outcome of women compared with men. In our analysis, had we not considered the interaction term of sex with age, we would have concluded that the older age of the women explains sex differences in mortality after MI, as many previous studies have.<sup>1</sup> However, inclusion of the interaction between sex and age in the model yielded a different final result.

To our knowledge, our study is the first to specifically address the hypothesis that mortality after MI of women compared with men differs according to age. However, this finding has been presented, somewhat unappreciated, in many previous studies<sup>3,8,13,14,23-25,34,35</sup> that showed age-stratified data. In all these studies, both unadjusted<sup>3,8,13,14,34,35</sup> and adjusted<sup>23-25</sup> differences in mortality between women and men (with women having

**Table 2. Relationship Between Sex and In-hospital Mortality After Myocardial Infarction for 2 Age Categories and Effect of Adding Covariables\***

	Age Group, y				P†
	<75		≥75		
	OR of Mortality for Female Sex	95% CI	OR of Mortality for Female Sex	95% CI	
Step 1, age adjusted	1.69	0.98-2.93	0.67	0.41-1.12	.01
Step 2, adjusted for age and comorbidity‡	1.52	0.86-2.68	0.65	0.39-1.08	.02
Step 3, adjusted for age, comorbidity, and clinical severity on admission§	1.56	0.87-2.79	0.61	0.36-1.04	.01
Step 4, adjusted for all above, plus process of care on admission  , hospital cardiovascular peer group, and hospital size ≥350 beds	1.49	0.82-2.71	0.54	0.30-0.94	.009
Reduced model¶	1.66	0.93-2.96	0.55	0.32-0.96	.004

\*The odds ratios (ORs) are calculated by means of logistic regression analysis. CI indicates confidence interval.

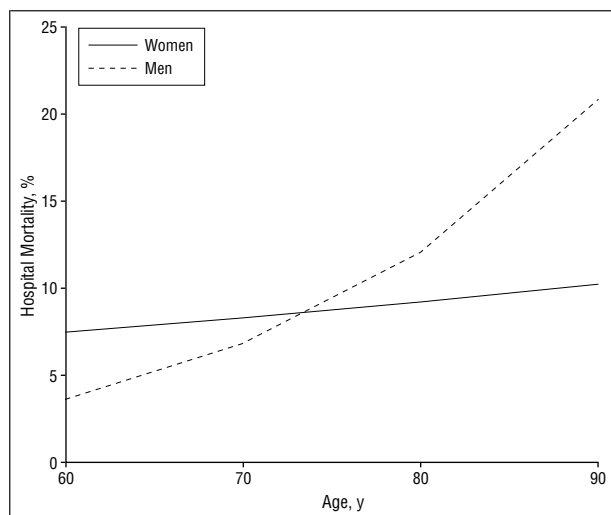
†P value for the integration effect: difference in OR for the association of sex with mortality rates between the 2 age groups.

‡History of congestive heart failure, history of cerebrovascular accident, history of diabetes treated with insulin, severe hypertension (history of uncontrolled hypertension or admission systolic blood pressure ≥200 mm Hg or diastolic blood pressure ≥120 mm Hg), renal dysfunction on admission (creatinine level, >176.8 μmol/L [>2 mg/dL]), and anemia on admission (hematocrit <0.3 or hemoglobin <0.01 g/L).

§Anterior infarction, Killip class III or IV, and first creatine kinase level more than 3 times the upper normal limit.

||Thrombolytic therapy within 24 hours from admission, aspirin, β-blockers, and angiotensin-converting enzyme inhibitors given within 24 hours from admission, and presence of a cardiologist as admitting or attending physician.

¶A backward elimination procedure was applied to the variables included in step 3, with significance level for remaining in the model of .05 for all variables in step 3 except sex, age, and the sex-age interaction that were forced. In addition to sex, age, and the sex-age interaction, the following variables were selected as a result of the backward elimination procedure: anterior infarction, Killip class III or IV, first creatine kinase level more than 3 times the upper normal limit, aspirin therapy within 24 hours from admission, and β-blocker therapy within 24 hours of admission. Similar results were obtained when the sex-age interaction was not forced in the model.



**Figure 2.** Predicted probability of in-hospital death from the logistic regression model (age ordinal) adjusted for all the variables in the most complete model of Table 2.

higher rates) were more pronounced in younger than in older age groups. For example, in the study by Kostis et al<sup>24</sup> death rates were significantly higher in women up to age 70 years, whereas after this age men had significantly higher rates. He et al<sup>23</sup> found a 3-fold difference in risk associated with sex between younger (<60 years) and older subjects in a study of patients with MI admitted to a Chinese hospital, and the authors concluded that the greater mortality of women compared with men was primarily attributable to sex differences in mortality at younger ages. In a sample of 1600 patients aged 30 to 74 years from the Minnesota Heart Survey, Demirovic et al<sup>25</sup> found that the 28-day mortality rate was twice as high in women than in men in multivariate analysis among patients younger than 65 years, while among older patients no differences in mortality were found. On the other hand, visual inspection of cumulative mortality curves in the Third International Study of Infarct Survival (ISIS-3) trial<sup>36</sup> indicates that the effect of sex on 35-day mortality was similar according to 3 age groups. However, because ISIS-3 was a randomized controlled trial, the generalizability of these results to the majority of patients with MI is unknown. In addition, unless the proportion of eligible patients who were included in the trial is the same in men and women, a bias with respect to sex in this type of study cannot be excluded.

Even among older populations the association between sex and mortality after MI appears to vary with age, albeit less strikingly so. An inspection of survival curves at 30 days in a large Medicare population<sup>21</sup> indicates that women had slightly higher mortality rates than men in the age group of 65 to 74 years, similar death rates in the age group of 75 to 84 years, and slightly lower mortality rates in the age brackets of 85 years or older. Among survivors of the first 30 days, women had overall a slightly lower 2-year mortality rate than men, but, again, the effect of sex on mortality appeared to depend on age: the older the age group, the greater the survival advantage of women.<sup>21</sup>

In our study the increased mortality in younger women compared with men occurred despite similar ad-

mission clinical severity characteristics. However, in the age group younger than 75 years women had a higher rate of comorbid conditions compared with men, while little difference in comorbidity was found among the older patients. Other studies have shown similar findings, in particular with regard to congestive heart failure,<sup>3,13</sup> diabetes mellitus, and renal insufficiency.<sup>25</sup> The higher prevalence of comorbidity (that may trigger complications during the hospital stay) in the younger women compared with men may also have contributed to the longer length of stay of these women. As expected from these sex differences in comorbidity distribution according to age, adjustment for concurrent illnesses partially explained the higher mortality of younger women compared with men, while it did not affect the relationship between sex and mortality in the older age group. However, inclusion of comorbid conditions in the analysis did not eliminate the interaction effect between sex and age. Consistent with our findings, Kostis et al<sup>24</sup> observed that the magnitude of difference between the adjusted and unadjusted relative risks was greatest in the youngest age group and least in the oldest, and that adjustment for comorbidity did not explain the higher mortality of women in the youngest age brackets.<sup>24</sup>

Why do women experience a more unfavorable outcome after MI in younger ages, but not at older ages? One explanation may be linked to the uncommon occurrence of MI in younger women. Because of the protective effect of estrogen in premenopausal ages, women are relatively spared from coronary atherosclerosis until about 75 years old.<sup>28</sup> Women who develop an MI prematurely may be those who are highly predisposed to this disease, either because of early onset and/or high severity of coronary heart disease risk factors, or because of genetic predisposition involving other mechanisms. For these same reasons the development of coronary artery disease may also be particularly aggressive in these women. Consistent with this hypothesis, we found higher rates of comorbidity and risk factors among women compared with men, but mostly limited to the younger age group. For example, women younger than 75 years had more than 2 times the rate of insulin-treated diabetes, stroke, and renal insufficiency, compared with men. The higher rate of diabetes, in particular, may have a genetic component and may lead toward severe atherosclerosis and cardiovascular events (including stroke), as well as renal insufficiency, which may in itself accelerate the atherosclerotic process. Genetic predisposition may involve other (yet less-defined) mechanisms. It has been demonstrated that the genetic susceptibility to coronary heart disease in women is strongest up to 75 years old and is independent of other risk factors for coronary heart disease.<sup>29</sup> While the evaluation of such genetic mechanisms is beyond the scope of our study, it is possible that heritable coagulation or metabolic factors may increase the risk of coronary heart disease in women particularly up to 75 years old. These same factors might be responsible for a worse prognosis of MI in these women. Several observations suggest that an increased liability for thrombosis and coronary artery spasm may play a greater role in the cause of MI in women, particularly if young or middle-aged, than in men.<sup>37-43</sup> These mechanisms may

be in part genetic in nature, may interact with standard coronary heart disease risk factors, and may put these women at a particularly high risk of death.

**A**NOTHER EXPLANATION may be a delay in detection of coronary heart disease in younger women. Some studies have indicated that women with symptoms of coronary heart disease are referred for cardiovascular procedures less often than men,<sup>44-46</sup> or that women are referred with more advanced disease.<sup>47</sup> Such phenomena may be most pronounced among young and middle-aged women, in whom coronary heart disease is relatively uncommon compared with men of similar age. This potential delay in the diagnosis and treatment of early manifestations of coronary heart disease may result in more severe MIs in these women compared with men. The finding that female patients with MI tend to have less advanced rather than more advanced coronary atherosclerosis than men<sup>35,39</sup> does not contradict this hypothesis, since severe infarctions may occur on mild or moderate lesions for which coronary collaterals have not been developed. However, a sex-related referral bias has been recently questioned by the finding that physicians do not appear to underestimate the risk of coronary disease in women when making a decision about referring patients for cardiovascular procedures.<sup>48</sup>

Another potential mechanism for the more unfavorable prognosis of women in the younger age group is lower use of established treatments for MI on admission, such as thrombolytic therapy, aspirin, and  $\beta$ -blockers. We observed a lower use of such therapeutic interventions in women compared with men, which was more pronounced at younger ages. Several studies<sup>34,50</sup> have found that recommended treatments for MI are administered less often to women<sup>49</sup> and to older patients, but sex differences in treatment have rarely been examined according to age. Gurwitz et al,<sup>50</sup> using the National Registry of Myocardial Infarction, presented data consistent with our results. In their study, the women in the age group younger than 55 years showed the lowest use of thrombolytic therapy and  $\beta$ -blockers compared with men. This finding of a greater treatment disparity in women compared with men at younger ages might reflect a lower suspicion of MI among younger women at presentation, or may be due to the more extensive comorbidity of these women compared with men of similar age. In our study these treatment differences appeared to contribute to the sex difference in mortality, although they did not explain it.

Our study presents several advantages compared with previous literature. We were able to examine the sex-age interaction on post-MI mortality while taking into account several factors that might influence it, ie, comorbidity, clinical severity, and process of care, in the attempt to explain this finding. Other advantages compared with some of the previous studies are the inclusion of study patients from several community hospitals rather than from a single institution, and the use of medical record abstraction data rather than administrative database information.

In interpreting the results of our study, we should take into account a number of methodological limitations. Information on coexisting illnesses was imperfect. Specifically, we did not have data on previous infarctions, or on the less severe forms of hypertension and diabetes. Incomplete measurement of comorbidity may be the reason why adjustment for concurrent illnesses did not eliminate women's higher risk of death in the younger age brackets. Nonetheless, previous studies<sup>23-25</sup> found higher mortality rates in nonelderly women compared with men even after controlling for these factors. Previous infarction is more common in men, therefore its inclusion may have decreased the survival advantage of women at older ages, but for the same reason it may have increased the female disadvantage at younger ages.

We should also acknowledge that, although we had more than a thousand patients in our analyses, our sample size did not allow to test for interactions with age that considered more than 2 age groups. The reason for this was the low mortality rates in the younger age groups. However, bivariate analyses showed a graded effect of sex on mortality between men and women according to age, which supported our initial hypothesis. Our sample size was also inadequate to assess sex differences within each age group. In fact, although the point estimates indicate a fairly large effect size (about 50% higher odds of mortality in women in the younger group, and, conversely, about 50% lower odds in women in the older group), the CIs included 1 in most models, particularly in the younger age group who had a lower mortality. Nonetheless, the main emphasis of this study was on sex differences across age groups rather than sex differences within age groups. Accordingly, the main result of our study is that mortality in women compared with men differs according to the patients' age, with a tendency for women to be disadvantaged compared with men among younger patients as opposed to older patients. A larger sample would be required to conclude that women have a significantly higher mortality rate than men in the younger age brackets.

Another potential pitfall is the exclusion of 80 patients because their outcome in the transfer hospitals was not known. Since there is no reason to suspect that these missing data were related to sex, they should not have introduced a bias in our analysis. On the other hand, the ability to consider outcome in transfer hospitals, in addition to the initial hospitalization, is a strength of our study and an improvement over previous research that has used hospital mortality as study outcome.

Given the sampling procedures, ie, inclusion of at least 50 cases from each of 15 hospitals of different sizes, our sample may have overrepresented patients from smaller hospitals. However, even though process of care (exemplified by use of thrombolytic therapy among eligible patients) varied among these hospitals,<sup>26</sup> it was not related to hospital size or presence of invasive cardiovascular services (unpublished data available from us). In addition, our study showed that the sex distribution in each age group did not vary by hospital size and cardiovascular services offered. Therefore, it is unlikely that the sampling procedures have biased our results.

Another limitation of our study is that we were able to include only individuals who were hospitalized for MI.

All individuals who died before reaching the hospital were not included. Yet this limitation is unavoidable if the diagnosis of MI has to fit accepted diagnostic criteria of clinical symptoms, enzyme elevations, and electrocardiographic changes. A study from the Scottish Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA)<sup>51</sup> project found that more men than women with coronary events die before reaching the hospital. Therefore, our observation of a higher in-hospital mortality among younger women may be due to a difference in prehospital mortality between younger men and women, with more women dying after hospital arrival because the equivalent number of men have already died before hospital arrival.<sup>51</sup> However, a more recent study<sup>30</sup> based on the whole MONICA registry involving populations in 18 different countries found similar median rates of prehospital death in men and women, with considerable variation of rates across countries.<sup>52</sup> While this possible explanation should be addressed by future studies, our investigation focuses on sex differences in outcome in that subgroup of patients with MI who make it to the hospital. We do not believe that the study of hospitalized individuals diminishes the importance of our findings, since these individuals may be more amenable to interventions to improve their outcome than those who die suddenly before being able to receive care.

In conclusion, our results suggest that the ongoing controversy about whether women fare worse than men after MI should be focused on women before elderly age. These women should be recognized as a particularly high-risk group for early mortality after MI compared with men. Among elderly patients, women may even show a survival advantage compared with men. This variation of effect of sex with age on postinfarction mortality may help resolve conflicting data on this topic in previous literature.

Our results have important implications for future research. When examining sex differences in outcome of MI, it may not be sufficient to adjust for age, but future studies should also consider the interaction between sex and age. Further investigations should also confirm our findings in larger populations, and address the mechanisms underlying the poor prognosis of nonelderly female patients with MI compared with men.

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For a complete list of the Myocardial Infarction Project II Steering Committee members see reference 26.

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