

The New England Journal of Medicine

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VOLUME 341

JULY 22, 1999

NUMBER 4



SEX-BASED DIFFERENCES IN EARLY MORTALITY AFTER MYOCARDIAL INFARCTION

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ABSTRACT

Background There is conflicting information about whether short-term mortality after myocardial infarction is higher among women than among men after adjustment for age and other prognostic factors. We hypothesized that younger, but not older, women have higher mortality rates during hospitalization than their male peers.

Methods We analyzed data on 384,878 patients (155,565 women and 229,313 men) who were 30 to 89 years of age and who had been enrolled in the National Registry of Myocardial Infarction 2 between June 1994 and January 1998. Patients who had been transferred from or to other hospitals were excluded.

Results The overall mortality rate during hospitalization was 16.7 percent among the women and 11.5 percent among the men. Sex-based differences in the rates varied according to age. Among patients less than 50 years of age, the mortality rate for the women was more than twice that for the men. The difference in the rates decreased with increasing age and was no longer significant after the age of 74 ($P < 0.001$ for the interaction between sex and age). Logistic-regression analysis showed that the odds of death were 11.1 percent greater for women than for men with every five-year decrease in age (95 percent confidence interval, 10.1 to 12.1 percent). Differences in medical history, the clinical severity of the infarction, and early management accounted for only about one third of the difference in the risk. After adjustment for these factors, women still had a higher risk of death for every five years of decreasing age (increase in the odds of death, 7.0 percent; 95 percent confidence interval, 5.9 to 8.1 percent).

Conclusions After myocardial infarction, younger women, but not older women, have higher rates of death during hospitalization than men of the same age. The younger the age of the patients, the higher the risk of death among women relative to men. Younger women with myocardial infarction represent a high-risk group deserving of special study. (*N Engl J Med* 1999;341:217-25.)

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WITH the recognition of cardiovascular disease as the number-one cause of death among women in the United States,¹ considerable interest has been focused on the study of sex-based differences in the outcome of myocardial infarction. However, after about a decade of research on this topic, studies are conflicting about whether short-term mortality after myocardial infarction is higher among women than men, after adjustment for differences in age and other prognostic factors.²⁻¹³

The traditional approach has been to compare men and women after adjustment for age and other covariables. However, younger women (those less than 65 or 70 years of age) who have a myocardial infarction may represent a distinct group in terms of risk factors and pathophysiology.¹⁴⁻¹⁹ We recently reported a significant interaction between sex and age with respect to short-term mortality after myocardial infarction.²⁰ The mortality rate among women younger than 75 years of age was twice that among men in that age group, whereas we found no differences in mortality among older patients. However, our previous study was limited by a sample size that allowed stratification into only two age groups.

The purpose of the present study was to confirm the hypothesis that age has a significant effect on

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*A complete list of the participating hospitals is available from ClinTrials Research, 1100 Weston Pkwy., Cary, NC 27513.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS, EARLY TREATMENTS, AND CHARACTERISTICS OF THE HOSPITALS IN THE ENTIRE GROUP AND ACCORDING TO AGE.*

CHARACTERISTIC	ALL PATIENTS†		AGE GROUP‡			
	WOMEN (N=155,565)	MEN (N=229,313)	30–59 YR	60–69 YR	70–79 YR	80–89 YR
	percent		odds ratio for characteristic			
Nonwhite race	16.0	15.2	1.41	1.32	1.18	1.03
Primary medical insurance						
Commercial or preferred provider organization§	12.0	24.1	1.00	1.00	1.00	1.00
Health maintenance organization	7.4	11.1	1.08	1.09	1.08	1.03
Medicare	67.2	48.8	1.51	1.52	1.38	1.38
Medicaid	3.7	2.6	2.77	2.90	1.90	1.53
Other	9.7	13.2	1.12	1.24	1.22	1.27
Medical history						
Previous myocardial infarction	24.4	28.3	0.80	0.72	0.70	0.73
Previous angina	18.4	17.6	1.03	0.92	0.91	0.90
Previous congestive heart failure	20.7	12.8	1.95	1.54	1.23	1.17
Previous coronary bypass	8.8	15.4	0.70	0.52	0.47	0.42
Previous coronary angioplasty	6.0	9.3	0.70	0.70	0.69	0.67
Previous stroke	11.2	8.4	1.73	1.23	1.02	0.91
Diabetes	33.1	24.8	2.14	1.67	1.30	1.11
Hypertension	59.3	47.1	1.45	1.46	1.53	1.66
Current smoker	18.8	29.3	0.90	0.96	0.90	0.59
Hypercholesterolemia	23.0	24.6	0.92	1.15	1.26	1.47
Diagnosis at admission						
Myocardial infarction or rule out myocardial infarction§	63.3	69.5	1.00	1.00	1.00	1.00
Unstable angina	10.6	12.1	1.06	0.92	0.87	0.84
Other	26.1	18.4	1.84	1.45	1.17	1.01
Clinical characteristics at admission						
Killip class						
1 (no heart failure)§	66.1	76.1	1.00	1.00	1.00	1.00
2 (heart failure)	21.4	15.4	1.51	1.35	1.16	1.06
3 (pulmonary edema)	10.5	6.9	1.95	1.57	1.23	1.13
4 (cardiogenic shock)	1.9	1.6	1.67	1.32	1.11	0.95
No chest pain	36.8	27.7	1.52	1.32	1.15	1.04
Systolic blood pressure (mm Hg)						
>120§	77.1	78.2	1.00	1.00	1.00	1.00
90–120	17.5	17.4	1.16	1.01	0.95	0.89
<90	5.5	4.4	1.72	1.27	1.06	0.94
Pulse >100 beats/min	29.0	21.8	1.62	1.47	1.20	1.14
Findings on initial electrocardiogram						
ST elevation	37.5	42.4	0.77	0.89	1.04	1.17
ST depression	27.9	28.2	0.97	1.01	1.06	1.00
Q-wave	10.2	11.7	0.77	0.88	0.96	1.07
Left bundle-branch block	7.8	5.8	1.44	1.19	0.98	0.98
Right bundle-branch block	5.1	7.0	0.79	0.63	0.56	0.52
Nonspecific changes	36.7	32.8	1.29	1.14	1.06	1.02
Time to presentation						
<2 hr§	29.4	36.8	1.00	1.00	1.00	1.00
2–6 hr	20.1	20.4	1.22	1.18	1.15	1.04
>6 hr	13.5	12.9	1.24	1.26	1.27	1.12
Unknown	37.0	29.9	1.52	1.39	1.28	1.11
Management in first 24 hours						
Thrombolytic therapy	16.2	22.5	0.75	0.84	0.94	0.98
Alternative reperfusion strategy	7.4	11.5	0.76	0.80	0.81	0.86
Aspirin	71.8	78.6	0.63	0.77	0.88	0.95
Intravenous beta-blockers	11.0	14.7	0.77	0.90	0.94	1.03
Oral beta-blockers	31.7	35.8	0.81	0.87	0.98	1.09
Angiotensin-converting–enzyme inhibitors	20.3	16.9	0.90	0.84	0.82	0.77
Characteristics of the hospitals						
No. of beds						
≤200§	26.7	24.2	1.00	1.00	1.00	1.00
201–400	44.9	45.1	0.99	0.97	0.99	1.02
401–600	18.9	20.1	0.99	0.95	0.95	0.98
>600	9.4	10.5	0.98	0.97	0.89	1.01
Facilities for cardiovascular procedures						
Cardiac surgery§	58.4	65.7	1.00	1.00	1.00	1.00
Cardiac catheterization without cardiac surgery	28.0	23.5	1.21	1.17	1.19	1.09
Neither	13.6	10.8	1.16	1.16	1.15	1.04

TABLE 1. CONTINUED.

CHARACTERISTIC	ALL PATIENTS†		AGE GROUP‡			
	WOMEN (N=155,565)	MEN (N=229,313)	30-59 YR	60-69 YR	70-79 YR	80-89 YR
	percent		odds ratio for characteristic			
Year of discharge						
1994§	10.7	11.0	1.00	1.00	1.00	1.00
1995	30.2	30.2	1.01	1.00	1.02	1.03
1996	32.4	32.3	1.02	1.02	1.00	1.02
1997-January 1998	26.7	26.5	1.04	1.00	1.01	0.97

*Percentages do not always total 100 because of rounding. P values are not reported because, given the large number of patients, assessing whether differences are statistically significant is not informative.

†The mean (\pm SD) age of the women was 72.4 ± 12.0 years, and the mean age of the men was 65.6 ± 13.1 years.

‡The respective numbers of women and men were as follows: 24,992 and 78,398 in the group that was 30 to 59 years of age, 30,524 and 55,615 in the group that was 60 to 69 years of age, 50,793 and 60,544 in the group that was 70 to 79 years of age, and 49,256 and 34,756 in the group that was 80 to 89 years of age. The odds ratio is for the comparison of women with men.

§This group was used as the reference category.

short-term mortality after myocardial infarction and to determine the reasons for this effect. We hypothesized that the younger the patients, the higher the risk of death during hospitalization among women relative to men.

METHODS

Patients

The National Registry of Myocardial Infarction 2 is a prospective, observational study of patients admitted to the hospital with acute myocardial infarction that was initiated on June 1, 1994. Participating hospitals enroll consecutive patients with acute myocardial infarction, as described previously.²¹ The methods of case ascertainment and data acquisition have been validated.²² By January 31, 1998, a total of 691,995 patients from 1658 U.S. hospitals had been enrolled. In the current analysis, we excluded 143,366 patients who were transferred from a participating hospital to another acute care institution, since the outcome after transfer was not known. We also excluded 886 patients with missing information on age, 16,925 patients who were 90 years of age or older, and 1189 patients who were less than 30 years of age, since myocardial infarction is rare in this age group, particularly among women. In our main analysis we also excluded 144,751 patients who had been transferred from other acute care hospitals, since admission data were often missing and, when they were not, they were thought to be less accurate. Therefore, 384,878 patients (155,565 women and 229,313 men) were included in this analysis. Since transferred patients accounted for 22 percent of all patients in the registry, and since more men (23.8 percent) than women (19.0 percent) had been transferred, we repeated the analyses with the sample that included patients who had been transferred to participating hospitals.

Clinical Variables

Information on clinical variables (Table 1) was abstracted from the medical records at each hospital.²¹ The degree of ventricular dysfunction was assessed with use of the Killip classification.²³

Statistical Analysis

First, we compared the mortality rate during hospitalization among women and men according to five-year age groups. We used the Breslow-Day test to assess whether there was an inter-

action between age and sex.²⁴ Next, we compared the base-line characteristics of the women and men, treatment factors, events that occurred during hospitalization, and characteristics of the hospitals with the use of four age groups (30 to 59 years, 60 to 69 years, 70 to 79 years, and 80 to 89 years). We then used a series of logistic-regression models to assess the effect of groups of variables on the associations of interest (sex and its interaction with age). We calculated odds ratios with their 95 percent confidence intervals from these models.

The first model included sex as an explanatory variable. In subsequent models, we added sequentially age, the interaction between sex and age, other demographic factors (race and insurance status), coexisting conditions (myocardial infarction, angina, congestive heart failure, stroke, coronary-artery bypass grafting, percutaneous transluminal coronary angioplasty, hypertension, diabetes, hypercholesterolemia, and current smoking), clinical indicators of the severity of the infarction, management in the first 24 hours after infarction, time from the onset of symptoms to presentation at the hospital, and characteristics of the hospitals. Each model also included three dummy variables for the year of discharge (1994, 1995, and 1996, with 1997-1998 used as the reference category). Given the large number of patients and the fact that all the candidate variables were deemed relevant, the size of the model was not reduced. In the case of two variables for which data were missing for at least 5 percent of patients — time to presentation (data missing for 33 percent) and left ventricular ejection fraction (data missing for 42 percent) — a dummy variable for the missing values was added to the models.

Age and its interaction with sex were modeled as continuous variables, since no significant departure from linear trend was found, consistent with the results of previous studies²⁵ and indicating an exponential increase in the odds of death with age. The odds of death for women as compared with men were calculated according to five-year decrements in age (from old to young). The adequacy of fit and the discriminatory power of the models were assessed according to standard methods.^{26,27} All tests of statistical significance were two-tailed.

RESULTS

Bivariate Analyses and Comparisons of Men and Women According to Age

As expected, the female patients were older than the male patients: the mean (\pm SD) age of the women

was 72.4 ± 12.0 years, whereas that of the men was 65.6 ± 13.1 years ($P < 0.001$). The mortality rate during hospitalization was higher among women than among men (16.7 percent vs. 11.5 percent; odds ratio for death among women as compared with men, 1.54; 95 percent confidence interval, 1.51 to 1.57). However, when the mortality rates were examined according to age group, sex-based differences varied according to age (Fig. 1). In the group of patients who were less than 50 years of age, the mortality rate during hospitalization was more than twice as high among the women. The difference in the rates decreased with increasing age and was no longer significant after the age of 74 ($P < 0.001$ for the overall interaction between sex and age).

Younger women were more likely than younger men to have diabetes, a history of congestive heart failure, and a history of stroke, but no sex-based differences were apparent at older ages (Table 1). At all ages men were more likely than women to have a history of myocardial infarction, coronary-artery bypass grafting, and coronary angioplasty and to be smokers. At younger ages women were more likely than men to be given a diagnosis other than myocardial infarction or unstable angina at admission, whereas the diagnoses at admission were similar among older men and women.

There were also age-related differences between men and women in the clinical characteristics at admission (Table 1). Younger women, but not older women, were more likely than men to have more se-

vere clinical abnormalities (i.e., higher Killip class, lower systolic blood pressure, and higher pulse rate), but they were less likely than their male peers to have chest pain and ST elevation on the initial electrocardiogram. Sex-based differences in treatment in the first 24 hours were small, but there was a consistent pattern of a lower likelihood of treatment among the women, in particular at younger ages. The characteristics of the hospital and the years of discharge were similar among the women and men.

Overall, the locations of the infarcts, creatine kinase levels, and left ventricular ejection fractions (among patients in whom ejection fraction was assessed) were similar among the women and men (Table 2). Nonetheless, younger women were more likely than younger men to have complications such as hypotension, heart failure, cardiogenic shock, and major bleeding and were less likely to undergo cardiovascular procedures such as coronary angiography and revascularization (Table 2).

Multivariable Analyses

Adjustment of the logistic-regression model for age appeared to account for most of the effect of sex on the mortality rate: the odds ratio for death among women decreased from 1.54 to 1.18 (95 percent confidence interval, 1.16 to 1.20). However, when the interaction between sex and age was included in the model, it was found to be significant ($P < 0.001$): for every five-year decrease in age, the odds of death during hospitalization for women relative to men in-

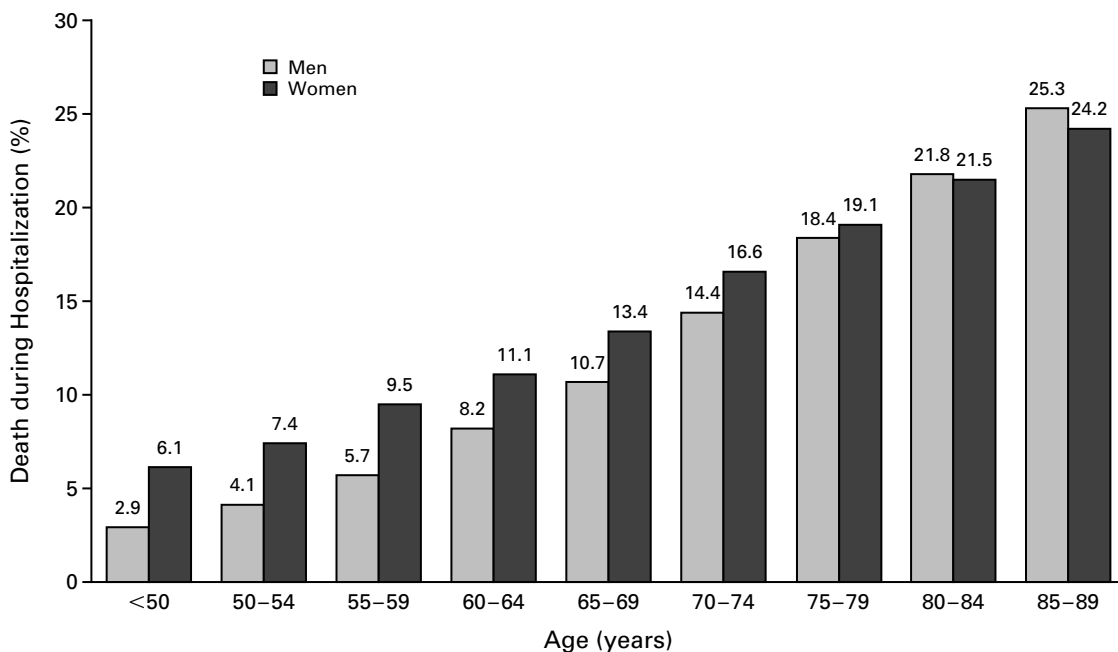


Figure 1. Rates of Death during Hospitalization for Myocardial Infarction among Women and Men, According to Age. The interaction between sex and age was significant ($P < 0.001$).

SEX-BASED DIFFERENCES IN EARLY MORTALITY AFTER MYOCARDIAL INFARCTION

TABLE 2. CHARACTERISTICS DURING HOSPITALIZATION IN THE ENTIRE GROUP AND ACCORDING TO AGE.*

CHARACTERISTIC	ALL PATIENTS		AGE GROUP†			
	WOMEN (N=155,565)	MEN (N=229,313)	30-59 YR	60-69 YR	70-79 YR	80-89 YR
	percent		odds ratio for characteristic			
Procedure						
Coronary angiography	28.7	39.5	0.90	0.84	0.82	0.77
Coronary-artery bypass grafting (other than immediate bypass)	5.9	9.5	0.72	0.74	0.68	0.65
Coronary angioplasty (other than primary angioplasty)	10.4	14.7	0.83	0.90	0.94	0.86
Mechanical ventilation	16.4	17.0	1.16	1.02	0.90	0.81
Clinical event						
Hypotension	16.9	14.7	1.37	1.19	1.04	1.00
Recurrent ischemia, angina, or myocardial infarction	11.1	10.7	1.10	1.09	1.09	1.14
Heart failure	23.2	16.3	1.65	1.39	1.15	1.09
Cardiogenic shock	7.1	5.5	1.64	1.28	1.07	0.97
Second- or third-degree atrioventricular block	4.1	3.3	1.34	1.26	1.08	1.07
Sustained ventricular tachycardia or ventricular fibrillation	6.2	7.8	0.96	0.86	0.74	0.68
Stroke or intracranial bleeding	0.6	0.4	1.74	1.53	1.37	1.15
Major bleeding (other than intracranial)	2.9	2.1	1.76	1.43	1.14	0.99
Other clinical data						
Location of infarct						
Anterior	27.0	25.8	1.02	1.00	1.11	1.10
Inferior	30.5	35.7	0.79	0.90	0.97	1.07
Posterior	4.4	5.6	0.78	0.85	0.91	0.96
Involvement of right ventricle	0.9	0.8	1.22	1.44	1.17	1.25
Unspecified or other location	39.3	34.5	1.35	1.13	0.98	0.89
Non-Q-wave myocardial infarction	55.3	50.5	1.32	1.15	1.00	0.90
Creatine kinase or creatine kinase MB ≥ 2 times normal range	81.5	84.8	0.78	0.82	0.85	0.87
Left ventricular ejection fraction						
$\geq 40\%$ ‡	38.6	42.1	1.00	1.00	1.00	1.00
$<40\%$	16.1	17.4	0.98	0.89	0.79	0.72
Not assessed	45.3	40.5	1.09	1.07	1.02	0.95

*P values are not reported because, given the large number of patients, assessing whether differences are statistically significant is not informative.

†The respective numbers of women and men were as follows: 24,992 and 78,398 in the group that was 30 to 59 years of age, 30,524 and 55,615 in the group that was 60 to 69 years of age, 50,793 and 60,544 in the group that was 70 to 79 years of age, and 49,256 and 34,756 in the group that was 80 to 89 years of age. The odds ratio is for the comparison of women with men.

‡This was the reference category.

creased 11.1 percent (95 percent confidence interval, 10.1 to 12.1 percent). Sex-based differences in medical history, clinical severity of the infarction, and early management accounted for about one third of the difference (Table 3 and Fig. 2). After adjustment for all the variables listed in Table 1, women still had a higher risk of death for every five-year decrement in age (increase in the odds of death, 7.0 percent; 95 percent confidence interval, 5.9 to 8.1 percent). The addition of the hospitals' characteristics to the model did not change the estimate for sex or for the interaction between sex and age. In every model the interaction between sex and age remained significant.

Previous studies have reported that diabetes may be a stronger prognostic factor after myocardial infarction in women than in men.^{28,29} Therefore, as a post hoc analysis, we checked whether there was a significant interaction between sex and diabetes with respect to the mortality rate in the age group in which most

sex-based differences in the rate were found (patients less than 70 years of age). No significant interaction between sex and diabetes was found (P=0.30).

The fit of the model appeared to be satisfactory. When the analyses were repeated in the group that also included the patients who had transferred to participating hospitals, the results were similar (data not shown).

DISCUSSION

Consistent with previous findings,^{5,7,30-43} we found that women as a group had a higher unadjusted risk of early death after myocardial infarction than men, and older age was an important potential explanation for this higher risk. However, examination of the results according to age revealed a different explanation. The risk among women was higher only before the age of about 75, was not accounted for by other characteristics in the analysis, and increased progres-

TABLE 3. VARIATION OF THE EFFECT OF SEX ON THE RISK OF DEATH DURING HOSPITALIZATION FOR EVERY FIVE-YEAR DECREMENT IN AGE AND THE EFFECT OF ADDING COVARIABLES.*

MODEL†	INCREASE IN ODDS OF DEATH % (95% CI)	P VALUE FOR SEX-AGE INTERACTION
Unadjusted	11.1 (10.1–12.1)	<0.001
Adjusted for race (white vs. nonwhite) and insurance status (Medicaid vs. all others)	10.9 (9.9–11.9)	<0.001
Adjusted for race, insurance status, and medical history (presence vs. absence)	9.8 (8.8–10.8)	<0.001
Adjusted for race, insurance status, medical history, and presence of clinical abnormalities	7.9 (6.8–9.0)	<0.001
Adjusted for race, insurance status, medical history, presence of clinical abnormalities, and management in first 24 hr (treatment vs. no treatment)	7.1 (5.9–8.2)	<0.001
Adjusted for race, insurance status, medical history, presence of clinical abnormalities, management in first 24 hr, and time to presentation (in 30-min increments)	7.0 (5.9–8.1)	<0.001

*Age was included as a continuous variable. The percentage increments in the odds of death for women as compared with men were calculated from the interaction between sex and age in each of the sequential models. Covariables were added sequentially, so that later models contain all the variables included in earlier models. CI denotes confidence interval.

†The unadjusted model included sex, age, the interaction between sex and age, and discharge year as three dummy variables (1994, 1995, and 1996, with 1997–1998 used as the reference category). Medical history was defined as a history of any of the following: myocardial infarction, angina pectoris, congestive heart failure, coronary-artery bypass grafting, coronary angioplasty, stroke, hypertension, diabetes, hypercholesterolemia, and current smoking. The clinical variables assessed at admission included Killip class (three dummy variables used for class II, III, and IV), chest pain on presentation (presence vs. absence), systolic blood pressure (an ordinal variable with three levels: <90, 90 to 120, and >120 mm Hg), pulse >100 beats per minute (vs. pulse ≤100 beats per minute), and abnormalities on the initial electrocardiogram (ST elevation, ST depression, Q waves, left bundle-branch block, right bundle-branch block, and nonspecific changes). Treatment in the first 24 hours included thrombolytic therapy, an alternative reperfusion strategy, aspirin, intravenous beta-blockers, oral beta-blockers, and angiotensin-converting-enzyme inhibitors. Time to presentation was entered in 30-minute increments. Missing data were coded as the lowest value, and a dummy variable for missing data was added to the model. The addition of the hospitals' characteristics to this model (number of beds and the presence of cardiac catheterization and of cardiac surgery facilities) did not change the results.

sively with decreasing age. This study confirms our preliminary report,²⁰ which was limited by the sample size. In both studies an elevated risk of early death among women relative to men gradually decreased with age and was seen only up to the age of approximately 75.

In line with epidemiologic,⁴⁴ pathological,¹⁶ and physiologic¹⁷ data, our results provide clinical evidence that women who have a myocardial infarction are a heterogeneous group; our findings thus further clarify whether female sex is a risk factor for short-term mortality after myocardial infarction. Studies of eld-

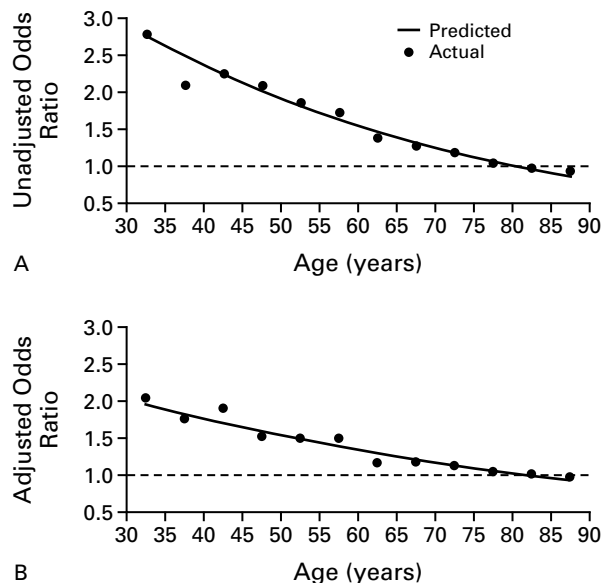


Figure 2. Odds Ratios for Death during Hospitalization for Myocardial Infarction in Women as Compared with Men, According to Age.

The unadjusted odds ratios (Panel A) were derived from the model that included sex, age, the interaction between sex and age, and the year of discharge. The adjusted odds ratios (Panel B) were derived from the model that also included race, insurance status, medical history, severity of clinical abnormalities at admission, type of management in the first 24 hours after admission, and time to presentation.

erly patients with myocardial infarction have consistently found either no significant differences in the mortality rate between men and women^{45,46} or a lower rate among women.^{47,48} In contrast, studies that have excluded elderly patients^{33,49,50} have tended to show higher mortality rates among women, even after adjustment for base-line differences. Most studies, however, included patients over a wide age range. The failure to account for a variation in the effect of sex according to age may have led to inaccurate risk estimates.

Studies based on patients who were enrolled in clinical trials^{5,10,11,49,50} or who met eligibility criteria for thrombolysis⁸ have also tended to show higher mortality rates during hospitalization or at one month among women than among men. For example, the Third International Study of Infarct Survival analyzed mortality data according to age and sex and found no interaction between sex and age.⁵ All the patients were seen within 24 hours after the onset of symptoms and had “clear indications” for thrombolytic therapy, as well as no contraindications. These selection criteria may explain in part the differences in results between those studies and our study. In our study younger women waited longer than men be-

fore going to the hospital, were less likely to be given a diagnosis of myocardial infarction at admission, and were less likely to receive thrombolytic therapy. Therefore, these women would most likely have been excluded from trials of thrombolytic therapy. Selection factors other than eligibility for treatment may also have a role, since a large proportion of eligible patients are usually not enrolled in randomized trials and certain types of patients are favored for inclusion.⁵¹

Epidemiologic data have indicated that women are relatively spared from coronary heart disease up to the age of 75.⁴⁴ Although the reasons for this protection are not entirely clear, estrogen is thought to play a part.⁵² Women in whom coronary atherosclerosis develops before the age of 75 may be predisposed to have particularly aggressive disease or possibly early onset or may have more risk factors for coronary heart disease, which might override the protective effect of estrogen. For example, diabetes has been found to negate the protective effect of female sex against coronary heart disease and death from cardiovascular disease^{53,54} and to be a stronger prognostic factor after myocardial infarction in women than in men.^{28,29} In our study, younger women, but not older women, were more likely to have diabetes than their male peers. The higher risk of diabetes was paralleled by a more frequent history of heart failure and stroke in younger women than in younger men. However, adjustment for diabetes and other coexisting conditions accounted for only about 10 percent of the difference in the risk, and there was no significant interaction between sex and diabetes.

Another possible explanation for the higher risk of death among younger women is the lower rate of use of established treatments for myocardial infarction, such as aspirin, beta-blockers, and thrombolytic therapy, in women.³ Sex-based differences in these treatments have been reported.⁵⁵⁻⁵⁷ In one study, female sex remained an independent predictor of the lack of use of reperfusion therapy among eligible patients.⁵⁷ However, after adjustment, treatment differences accounted for only about 10 percent of the effect of the interaction between sex and age in our study, possibly because the severity of the clinical abnormalities was already in the model. The latter variable had the strongest impact, accounting for 19 percent of the effect of the interaction between sex and age.

The pathophysiology of coronary heart disease in premenopausal or middle-aged women may differ from the more common disease of older women and of men. Plaque erosions are the predominant abnormality in premenopausal women who die suddenly, whereas rupture of plaques is more common in older women and in men.¹⁶ In addition, younger women who have a myocardial infarction,¹⁴ who die suddenly of coronary causes,¹⁶ or who survive a cardiac arrest¹⁵ have less narrowing of the coronary arteries than older women or men. These findings suggest that dif-

ferent clotting mechanisms may trigger myocardial infarction in younger women, perhaps involving a hypercoagulable state or coronary spasm. Young women who survive myocardial infarction have more reactive platelets than young male survivors,¹⁷ and transmural myocardial infarction with normal findings on coronary angiography, which is distinctly more common in young women, has been associated with vasospastic syndromes such as migraine and Raynaud's phenomenon, as well as hypercoagulable states such as pregnancy and use of oral contraceptives.¹⁸ These and other mechanisms may be genetic in nature or have a genetic predisposition. A family history of death from coronary heart disease is associated with an increased risk of this event in both men and women, but this susceptibility is stronger in younger women than in older women or in men.⁵⁸

It is also possible that the higher rate of death during hospitalization among younger women is due to sex-based differences in the mortality rate before hospitalization. Studies of two registries participating in the World Health Organization's Monitoring Trends and Determinants in Cardiovascular Disease Project,^{42,43} which assesses coronary events in people less than 64 years of age, have shown that a higher rate of death from myocardial infarction during hospitalization among women is balanced by a higher rate of death before hospitalization among men. However, a study of the project's entire registry, involving 29 populations in 18 countries, found considerable variation in the rates of death before hospitalization.¹³ Therefore, this issue needs further clarification.

The peculiar characteristics of coronary heart disease in young and middle-aged women may have diagnostic implications that affect management decisions and, therefore, prognosis. The less extensive narrowing of coronary arteries in these women may cause underdiagnosis of coronary heart disease with the use of traditional diagnostic tests such as coronary angiography. Studies have suggested that women with symptoms of coronary heart disease are referred for cardiovascular procedures less often⁵⁹⁻⁶¹ or later⁶² than men. Some of these differences may reflect differences in the characteristics of early manifestations of coronary heart disease in women, as suggested by our findings of age-based differences in the presentation of myocardial infarction. If the early symptoms, signs, and pathophysiology of coronary heart disease in women differ from those in men, the condition may be more difficult to recognize in women at an early stage.

A strength of our study, in addition to the use of a large number of patients from several states, is its observational design. Consent procedures or eligibility for treatment was not required for enrollment, therefore minimizing bias and increasing the generalizability of results. Although the data we collected were not independently validated, our methods of

case ascertainment and acquisition of other data have been found to be valid.²² In addition, the simplicity of the protocol enabled us to assemble one of the largest and most contemporary data bases of myocardial infarction in the United States. Although the use of death during hospitalization as the end point (with an average length of stay of about 7 days) may decrease the comparability of our results with those of other investigations that have used 28-to-35-day mortality as the end point,^{4,5,7,43} most deaths after hospital admission for myocardial infarction occur early, most commonly in the first 24 hours.¹³

In conclusion, we found that the higher short-term mortality of women, as compared with men, after myocardial infarction was confined to women who were less than 75 years of age — the age group in which myocardial infarction can be considered premature in women. In addition, the younger the age of the women, the higher the risk of death relative to men. This higher risk was only partially accounted for by differences in coexisting conditions, clinical characteristics, and early management. Our results indicate that younger women with myocardial infarction are a high-risk group deserving of special study and that patients' age must be considered in assessments of sex-based differences in short-term mortality after myocardial infarction.

Dr. Krumholz is a Paul Beeson Faculty Scholar.

We are indebted to Dr. Judy Malmgren for her expertise in the management of study data.

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