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Sex Differences in 2-Year Mortality after Hospital Discharge for Myocardial Infarction

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Background: An interaction between sex and age is thought to affect hospital mortality after myocardial infarction; younger, but not older, women have been shown to have higher mortality rates than men. It is currently unknown whether findings are similar after hospital discharge.

Objective: To determine whether an interaction between sex and age affects 2-year mortality after myocardial infarction.

Design: Community-based prospective cohort study.

Setting: 16 community hospitals serving the Worcester, Massachusetts, metropolitan area.

Patients: 6826 patients who survived hospitalization for acute myocardial infarction during ten 1-year periods between 1975 and 1995.

Measurements: Mortality 2 years after hospital discharge.

Results: The overall 2-year mortality rate was higher in women (28.9%) than in men (19.6%). When patients were examined by age group, however, only women younger than 60 years of age had a higher mortality rate than men of similar age. The sex difference decreased with increasing age; among the oldest patients, women had a lower mortality rate than men ($P = 0.009$ for the interaction between sex and age). This relationship was not affected by adjustment for demographic characteristics and medical history, clinical characteristics, and hospital and discharge treatments; the hazard of 2-year death for women compared with men increased 15.4% (95% CI, 4.3% to 27.6%) for every 10-year decrease in age. In absolute terms, after adjustment for demographic characteristics and medical history, among patients younger than 60 years of age women were at greater risk than men (risk difference, 1.8 percentage points). At older ages, however, women were at lower risk than men.

Conclusions: Younger, but not older, women who survive hospitalization for myocardial infarction have a higher long-term mortality rate than men. This provides additional evidence that younger women with myocardial infarction are at greater risk for death than men.

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The issue of whether women have more unfavorable short-term outcomes than men after acute myocardial infarction has elicited considerable debate (1–6). In a recent study, we demonstrated an important interaction between sex and age that affected hospital mortality after myocardial infarction (7, 8). We found that younger, but not older, women have higher mortality rates than men of similar age. The risk among women increases linearly with decreasing age and is not fully explained by differences in clinical presentation or treatment (8).

In contrast to short-term mortality studies, most studies examining long-term outcomes among survivors of the acute phase (hospitalization or the first month thereafter) have generally found no differences in mortality between men and women, and some have found that women have a more favorable outcome (5, 6, 9–22). However, these studies did not examine whether the association of sex with mortality changes according to age. An increased long-term risk for death among younger women may well be masked by the combined examination of all age groups.

We examined survivors of the acute infarction episode to determine whether younger, but not older, women have a greater risk for death after hospital discharge than men of similar age. The Worcester Heart Attack Study is an ideal population in which to test this hypothesis, since it is a large community-based registry that involves long-term follow up of patients of different ages.

Methods

Study Sample

The study sample consisted of 8277 residents of the Worcester, Massachusetts, standard metropolitan statistical area who were hospitalized for a confirmed myocardial infarction in any of the 16 community and teaching hospitals serving this region during 10 calendar years (1975, 1978, 1981, 1984, 1986, 1988, 1990, 1991, 1993, and 1995). All hospitals in this geographic area participated in this study. The medical records of all patients who were assigned a primary or secondary discharge diagnosis of myocardial infarction were individually reviewed, and the diagnosis was confirmed according to preestablished criteria, as described elsewhere (16, 23, 24). Cases of perioperative myocardial infarction were not included.

For the analysis of long-term survival after discharge, we excluded 1366 patients who died during the index hospitalization. An additional 85 patients (1.2% of the hospital survivors) were excluded because vital status at follow-up was unknown. Therefore, 6826 patients who survived the index hospitalization were available for analysis.

Data Collection

Demographic characteristics, medical history, clinical characteristics of the infarction, hospital complications, and use of treatments and interventional procedures were abstracted from the medical records as described elsewhere (16, 24–27). Vital status after discharge was ascertained by a review of medical records for subsequent hospitalizations and a statewide and national search of death certificates for metropolitan Worcester residents (23, 24, 27). The outcome of our study was survival status 2 years after hospital discharge, since all patients in the current analysis had reached at least the 2-year anniversary.

Statistical Analysis

Before excluding in-hospital deaths, we compared hospital mortality in women and men according to 10-year age groupings. The effect of the interaction between age and sex on hospital mortality was tested in a logistic regression model by using the likelihood ratio test.

In the sample of hospital survivors, we compared baseline characteristics, hospital events, and treatments between women and men in three collapsed age groups (<60 years, 60 to 69 years, ≥70 years) that corresponded to approximate tertiles of the age distribution. Collapsed age groups were used to allow sufficient cell numbers for all comparisons. We used life-table methods (28) to compare cumulative all-cause mortality from hospital discharge to 2 years after stratification according to the three age groups.

Finally, to assess the impact of groups of variables on the associations of interest (sex and the effect of its interaction with age on mortality), we conducted a series of Cox proportional hazards regression models for 2-year mortality after hospital discharge. Hazard ratios and accompanying 95% CIs for sex were calculated according to age from the Cox models.

The first model included sex and age as explanatory variables. In the second model, the interaction between sex and age was added. In a subsequent model, we added other demographic factors (ethnicity and marital status) and medical history (history of infarction, angina, congestive heart failure, diabetes, stroke, and hypertension). In a final model, we added clinical characteristics of the infarction (Q-wave infarction and anterior infarction), hospital complications (congestive heart failure, cardiogenic shock, stroke, atrioventricular block, and ventricular tachycardia or fibrillation), hospital treatments and procedures (thrombolytic therapy, coronary angiography, coronary bypass, and coronary angioplasty), and discharge treatments (antiplatelet medications, β-blockers, diuretics, digoxin, angiotensin-converting enzyme inhibitors, calcium-channel blockers, and nitrates). Potential confounding by hospital and by discharge year were addressed by refitting the final model with these variables, respectively, as stratification factors. Because studies have reported that diabetes may be a stronger risk factor for death in women than in men after myocardial infarction (29–32), the effect of the interaction between sex and diabetes on mortality rate was also tested.

Linearity of age and of the interaction between age and sex was checked by fitting age and the age–sex interaction both as categorical variables and as linear terms in the proportional hazards models. Age and its interaction with sex were ultimately modeled as continuous variables (in years) because no significant departure from linear trend was found. The hazard ratio of 2-year death for women compared with men was calculated according to 10-year age decrements (from old to young).

Multivariable results were also examined in terms of risk differences between men and women according to age by deriving the predicted probabilities at 24 months from Cox proportional hazards models in the three age groups. Covariable levels were standardized to the distribution of the entire study sample (33). To avoid model overfitting, given the smaller sample size in the age-stratified models, control factors in these analyses were limited to demographic characteristics and medical history.

The proportional hazards assumption was checked by testing the significance of the interaction between main predictor variables and time. All tests of statistical significance were two tailed, and all analyses were performed by using SAS, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Results

Hospital Mortality

Of 8277 patients with confirmed acute myocardial infarction, 1366 died during the index hospitalization. Overall, the hospital mortality rate was significantly higher in women (20.9%) than in men (13.6%) ($P = 0.01$). As expected, sex differences in hospital mortality varied according to age. In persons younger than 50 years of age, women had an almost threefold higher risk for death than men. The odds ratio of hospital death for women compared with men decreased with advancing age and was close to 1.00 among patients at least 70 years of age.

Baseline Sex Differences in Hospital Survivors

Among the 6826 hospital survivors with known vital status at follow-up, women were significantly older than men overall (mean age, 71.4 years vs. 63.2 years; $P < 0.001$). In all age groups, women were less likely to be married and more likely to have a history of heart failure and hypertension (**Table 1**). Younger women, but not older women, were more likely than men of similar age to have a history of diabetes and stroke and to have experienced an anterior infarction during the index admission. However, at all ages, men were more likely than women to have a history of myocardial infarction and to have had a Q-wave infarction during the index hospitalization. Women, especially those younger than 60 years of age, experienced more heart failure and heart block, but men more often had complicating ventricular arrhythmias during the index hospitalization. Sex differences in treatments and procedures during hospitalization were small. At discharge, women were less likely than men to be prescribed β-blockers but were more likely to receive diuretics and digoxin. Similar proportions of men and women were included in different discharge years.

Sex Differences in 2-Year Mortality among Hospital Survivors

At 2 years after hospital discharge, 1577 patients had died (748 women [28.9%] and 829 men [19.6%]; hazard ratio for women compared with men, 1.47 [95% CI, 1.35 to 1.61]). However, when patients were examined by age group (**Table 2** and **Figure**), only women younger than 60 years of age had a higher mortality rate than men of similar age. Sex differences in mortality rate decreased with advancing age, and among the oldest patients, women tended to have lower mortality rates than men. Results were consistent when examined in terms of risk difference (**Table 2**). The absolute risk for women compared with men was highest in patients younger than 60 years of age, while the absolute risk was lower for women among patients at least 80 years of age. As expected, given the higher mortality rates of older patients, the risk difference between women and men at older ages was larger than the risk difference at younger ages. Because women were older than men within each age interval shown in the **Figure**, the curves for cumulative mortality rate were adjusted for age (with age as a continuous variable). The hazard ratio of death for women compared with men was 1.40 in those younger than 60 years of age, 1.05 in those 60 to 69 years of age, and 0.95 in those at least 70 years of age.

When we adjusted for age in a Cox proportional hazards model, it seemed to explain the overall sex difference in 2-year mortality rate, yielding a hazard ratio of 1.00 (CI, 0.90 to 1.12). However, when the interaction between sex and age was included in the model, it was found to be statistically significant (**Table 3**). For every 10-year decrease in patients' age, hazards of death in women increased 13.1% (CI, 3.1% to 23.9%) compared with men.

Table 3 shows the effect of adjustment for baseline characteristics on the interaction between sex and age. Adjustment for covariables did not materially affect sex differences in mortality according to age. In the fully adjusted model, for every 10 years of decreasing age, the hazards for women compared with men increased 15.4% (CI, 4.3% to 27.6%; $P = 0.005$). When the sex-related risk for death was calculated from the model results according to age, women had a greater risk for death before approximately 60 years of age, had approximately the same risk between 60 and 70 years of age, and tended to have lower risk after 70 years of age. In

Table 1. **Comparison of Baseline Characteristics between Women and Men according to Age**

Characteristic	<60 Years		60–69 Years		≥70 Years	
	Women (*n* = 422)	Men (*n* = 1596)	Women (*n* = 593)	Men (*n* = 1234)	Women (*n* = 1577)	Men (*n* = 1404)
Demographic data						
Median age (range), *y*	53 (23–59)	51 (19–59)	65 (60–69)	64 (60–69)	78 (70–98)	76 (70–97)
Nonwhite ethnicity, %	5.6	5.4	4.2	3.8	1.8	1.9
Married, %	66.1	81.6	57.3	83.6	28.4	71.5
Medical history, %						
Myocardial infarction	20.1	24.9	31.0	37.4	36.2	41.2
Angina	19.2	19.5	26.5	25.2	31.5	33.8
Heart failure	6.2	3.7	14.0	9.6	26.0	18.2
Stroke	4.0	2.0	6.9	5.9	11.0	12.1
Hypertension	44.8	39.4	58.3	50.0	61.7	49.0
Diabetes	27.7	14.5	32.7	24.2	28.6	25.6
Characteristics of myocardial infarction, %						
Q-wave	55.7	62.4	48.6	52.1	38.7	44.9
Anterior	46.9	39.5	44.6	40.6	48.2	47.6
Hospital complications, %						
Heart failure	28.9	20.7	39.5	33.6	55.4	45.8
Cardiogenic shock	2.8	2.3	2.5	2.1	2.9	1.8
Second- or third-degree atrioventricular block	9.5	5.5	6.9	6.2	5.7	7.7
Ventricular tachycardia or fibrillation	19.2	24.5	15.7	20.8	11.8	17.2
Treatments and procedures during hospitalization, %						
Thrombolytic therapy	19.2	22.3	16.4	16.0	8.1	9.1
Coronary angiography	28.0	28.3	20.9	24.7	10.0	17.0
Coronary bypass	1.7	2.5	2.9	2.8	1.1	1.8
Coronary angioplasty	7.8	8.1	5.4	4.3	2.4	3.3
Treatments at discharge, %						
Antiplatelet medications	36.0	40.1	36.6	38.2	37.1	36.9
β-Blockers	44.6	55.9	41.2	45.7	35.4	36.2
Angiotensin-converting enzyme inhibitors	5.0	5.8	9.4	7.5	14.0	12.8
Calcium-channel blockers	42.6	37.0	40.4	41.1	40.9	42.5
Nitrates	63.3	60.6	58.4	62.8	67.9	65.5
Diuretics	18.3	10.5	26.1	20.3	40.6	33.0
Digoxin	13.3	10.1	21.4	22.3	35.5	32.3
Discharge year, %						
1975 or 1978	24.2	22.5	19.8	19.9	14.8	13.9
1981 or 1984	20.9	21.3	20.9	20.4	20.2	18.1
1986 or 1988	15.8	17.8	17.8	18.7	17.5	16.5
1990 or 1991	17.8	16.4	19.1	20.1	20.6	23.7
1993 or 1995	21.4	22.0	22.5	20.9	27.0	27.8

the last model in **Table 3** (which was adjusted for demographic characteristics, medical history, clinical characteristics of the infarction, hospital complications, hospital treatments and procedure, and discharge treatments), the 2-year mortality hazards for women compared with men were 1.42 at 40 years of age, 1.23 at 50 years of age, 1.07 at 60 years of age, 0.92 at 70 years of age, and 0.80 at 80 years of age. After the final model was refitted with hospital as a stratification factor to address potential confounding, it yielded virtually identical results. For every 10-year decrease in age, the hazards for women increased 15.6% (CI, 4.5% to 27.8%) compared with men. When discharge year was used as a stratification factor to address potential confounding, results were also very similar. The incremental hazard for women per 10-year decrease in age was 15.9% (CI, 4.8% to 28.3%) compared with men. We found that the interaction between sex and diabetes did not have a statistically significant effect on mortality.

When the multivariable-adjusted results were expressed in terms of absolute risk difference, an increased mortality rate among women compared with men was found only among patients younger than 60 years of age. Among older patients, women had a lower absolute risk for death than men. The risk difference comparing women with men, adjusted for demographic characteristics and medical history, was 1.8 percentage points in those younger than 60 years of age, −1.7 percentage points in those 60 to 69 years of age, and −3.4 percentage points in those at least 70 years of age. Because mortality rates increase considerably with age, sex differences in absolute mortality risk at older ages are expected to be larger than those at younger ages.

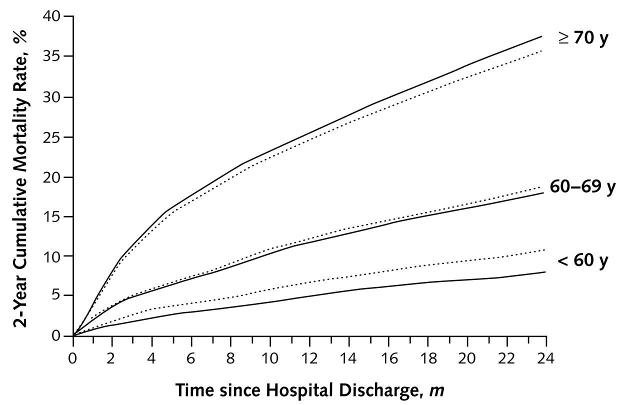
Discussion

The results of this multihospital community-based study demonstrate that among survivors of the index hospitalization, the interaction between sex and age has an important effect on long-term mortality rate after myocardial infarction. Women younger than 60 years of age had a higher mortality rate than men. The mortality risk for women compared with men decreased as age increased, to the point that women among the oldest patients tended to have a lower 2-year mortality rate than men of similar age. The difference in mortality according to age persisted after adjustment for medical history, clinical severity at the time of hospitalization, hospital complications, hospital treatments and procedures, and discharge treatments.

It is remarkable that the effect of the interaction between sex and age on 2-year mortality after hospital discharge occurred independently of a similar interaction involving hospital mortality. The latter interaction was also observed in this cohort, consistent with previous reports (7, 8). Better selective survival could have been expected among younger women after discharge, since more younger women (presumably those at highest risk) died during hospitalization than younger men.

Most studies of sex differences in long-term mortality among survivors of the acute postinfarction period have found either no differences in mortality between men and women (9–11) or even lower mortality in women than in men (5, 6, 12–18). When a higher mortality rate in women was initially found, it was usually explained by age alone or in combination with other prognostic factors (5, 10, 11). Consistent with these previous observations, in our study age alone initially seemed to explain the sex differences in mortality in the sample as a whole, reducing the hazard ratio for the entire group of women compared with the entire group of men from 1.47 to 1.00. However, examination of results according to specific age strata revealed that the effect of sex on mortality varied according to age.

Figure. **Age-adjusted cumulative mortality rate from hospital discharge to 2 years in three age groups.**



Solid lines represent men; dotted lines represent women.

Other studies that examined long-term mortality after myocardial infarction have not usually investigated the presence of an interaction between sex and age. Three studies, however, presented results after age stratification (12, 19, 22). Of these, two showed data consistent with an interaction between sex and age; however, the authors did not emphasize this point. Kostis

Table 2. **Distribution of Deaths from Discharge to 2 Years, Hazard Ratio, and Risk Difference among Women and Men**

Age Group	Women			Men			Hazard Ratio	Risk Difference
	Total Patients	Deaths	Mortality Rate	Total Patients	Deaths	Mortality Rate		
	n		%	*n*		%		*percentage points*
<50 y	135	12	8.9	668	40	6.0	1.48	2.9
50–59 y	287	33	11.5	928	77	8.3	1.39	3.2
60–69 y	593	109	18.4	1234	212	17.2	1.07	1.2
70–79 y	875	271	31.0	985	285	28.9	1.07	2.1
≥80 y	702	323	46.0	419	215	51.3	0.90	−5.3

Table 3. **Multivariable Analysis of the Effect of Sex on Risk for Death 2 Years after Hospital Discharge for Every 10-Year Decrease in Age***

Model†	Increase in the Hazard for Death in Women Compared with Men (95% CI), %	*P* Value for Sex–Age Interaction
Unadjusted	13.1 (3.1–23.9)	0.009
Adjusted for demographic factors and medical history	14.7 (4.0–26.5)	0.006
Adjusted for demographic factors, medical history, clinical characteristics of the infarction, hospital complications, hospital treatments and procedures, and discharge treatments	15.4 (4.3–27.6)	0.005

* Age was included as a continuous variable (in years). The increments in the risk for women compared with men were calculated from the sex–age interaction in each of the sequential models and express the increase in risk for women compared with men for every 10-year decrease in age. Covariables were added sequentially; later models contain all the variables included in earlier models.
† The unadjusted model included sex, age, and the interaction between sex and age. Demographic characteristics, in addition to age, included ethnicity and marital status. Medical history included history of infarction, angina, heart failure, diabetes, stroke, and hypertension. Clinical characteristics of the infarction included Q-wave infarction and anterior infarction. Hospital complications included congestive heart failure, cardiogenic shock, stroke, atrioventricular block, and ventricular tachycardia or fibrillation. Hospital treatments and procedures included thrombolytic therapy, coronary angiography, coronary bypass, and coronary angioplasty. Discharge treatments included antiplatelet medications, β-blockers, diuretics, digoxin, angiotensin-converting enzyme inhibitors, calcium-channel blockers, and nitrates.

and coworkers (22) reported that higher mortality rates at 3 years after myocardial infarction in women compared with men were present only up to 70 years of age. The mortality data in their study, however, also included in-hospital deaths. In a large Medicare population, the effect of sex on long-term mortality after myocardial infarction varied slightly according to age, despite the fact that the sample included only older adults (12). A third study (19), however, showed a similar sex-based difference in mortality rate in four age groups, although the number of women, particularly younger women, was small.

We found that preexisting illnesses and risk factors, myocardial infarction characteristics, acute clinical complications, and treatments did not explain the higher postdischarge mortality differences in younger women compared with men. In addition, a possible effect of diabetes in women and men, previously suggested in the literature (29–32), did not play a role in our findings. In our previous report of hospital mortality, differences in medical history, clinical characteristics, and treatments between women and men explained only approximately one third of the sex-based mortality differences at younger ages (8). In addition, no interaction between sex and diabetes was found (34). Our current analysis indicates that these factors may have an even smaller effect on sex-based mortality differences after discharge. Therefore, other explanations should be sought.

Compared with men, women are more protected against coronary atherosclerosis until their later years of life, as indicated by a lower incidence of myocardial infarction (35), a greater likelihood of unstable angina as the initial manifestation of acute cardiac ischemia (36–41), and less extensive coronary narrowing at the time of the acute ischemic episode (10, 38, 42–44). This apparent protection raises the question of whether younger women who experience a myocardial infarction have some unknown risk factors or lack protective factors normally present in women (45).

Proposed mechanisms for premature coronary heart disease in women have focused on estrogen mechanisms (such as abnormalities in the density or type of estrogen receptors [45, 46]) or indices of ovarian dysfunction (such as lower estrogen levels [47], menstrual irregularities [48–50], and premature menopause [51, 52]). In addition to increasing women's risk for premature coronary heart disease, these mechanisms might also impair the ability of women to repair myocardial damage once it has occurred, leading to increased long-term mortality. These hypotheses, however, are not necessarily useful in explaining why women have higher mortality rates than men after myocardial infarction; if they are correct, the risk between men and women would be equalized because the female survival advantage would be eliminated.

Because the sex-based differences in mortality were independent of clinical severity and other clinical characteristics, nonbiological factors might be implicated. Behavioral, psychological, and social factors should be considered as alternative explanations. For example, depression (53, 54), social isolation and lack of support (55–57), low socioeconomic resources (58, 59), and various definitions of "emotional stress" (60–62) have been related to prognosis after coronary heart disease and may affect women and men differently. Psychosocial factors might play a role by influencing lifestyle and health behaviors (such as smoking, adherence to medications, and propensity to seek medical care) but also by influencing several pathophysiologic pathways implicated in coronary ischemia and arrhythmogenesis (63).

Another possible explanation for our findings is a difference in the threshold for hospital admission. Because acute coronary ischemia is less typical in women than in men, particularly at younger ages (8), it is possible that milder cases of myocardial infarction are more often missed in women. This would artificially increase the proportion of severe cases in women who are admitted to the hospital. Since our study was based on hospitalized patients, we could not assess whether sex differences in the likelihood of being admitted affected our results. However, data from the multinational Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA) project have shown that consideration of out-of-hospital deaths did not eliminate the higher hospital case fatality among female patients younger than 50 years of age (64).

Another limitation of our study is that the available information included only data abstracted from medical records. No information was available about reproductive history, menopausal status, or behavioral and psychosocial factors. We also did not have information on current or previous smoking status. Although smoking status seems to be similar in male and female patients with myocardial infarction who are younger than 70 years of age (3, 8), women might be less prone to stop smoking after myocardial infarction than men. In addition, we did not have information on the use of outpatient treatments during follow-up, adherence to medications, and referral and adherence to cardiac rehabilitation programs. Each of these factors could explain the mortality differences observed if they differ between women and men, particularly at younger ages. Despite these limitations, however, this study has the important strengths of being community-based in a large metropolitan area. This should minimize bias and ensure the generalizability of the results.

In summary, we found that an important interaction between sex and age affected long-term mortality among survivors of hospitalization for myocardial infarction. These findings complement a similar recent finding regarding hospital mortality (8). Our results underscore the fact that younger women who develop a myocardial infarction are at greater risk for death than younger men with the same condition. Future research should examine the reasons for this increased mortality. Increased understanding will provide important insights into the pathophysiology and clinical course of cardiovascular disease in women, as well as the development of more effective secondary preventive approaches.

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References

1. **Vaccarino V, Krumholz HM, Berkman LF, Horwitz RI.** Sex differences in mortality after myocardial infarction. Is there evidence for an increased risk for women? Circulation. 1995;91:1861-71. [PMID: 0007882498]

2. **Nohria A, Vaccarino V, Krumholz HM.** Gender differences in mortality after myocardial infarction. Why women fare worse than men. Cardiol Clin. 1998;16: 45-57. [PMID: 0009507780]

3. **Malacrida R, Genoni M, Maggioni AP, Spataro V, Parish S, Palmer A, et al.** A comparison of the early outcome of acute myocardial infarction in women and men. The Third International Study of Infarct Survival Collaborative Group. N Engl J Med. 1998;338:8-14. [PMID: 0009414325]

4. **Marrugat J, Sala J, Masia R, Pavesi M, Sanz G, Valle V, et al.** Mortality

differences between men and women following first myocardial infarction. RESCATE Investigators. Recursos Empleados en el Sindrome Coronario Agudo y Tiempo de Espera. JAMA. 1998;280:1405-9. [PMID: 0009800999]

5. **Maynard C, Every NR, Martin JS, Kudenchuk PJ, Weaver WD.** Association of gender and survival in patients with acute myocardial infarction. Arch Intern Med. 1997;157:1379-84. [PMID: 0009201013]

6. **Kober L, Torp-Pedersen C, Ottesen M, Rasmussen S, Lessing M, Skagen K.** Influence of gender on short- and long-term mortality after acute myocardial infarction. TRACE study group. Am J Cardiol. 1996;77:1052-6. [PMID: 0008644656]

7. **Vaccarino V, Horwitz RI, Meehan TP, Petrillo MK, Radford MJ, Krumholz HM.** Sex differences in mortality after myocardial infarction: evidence for a sex-age interaction. Arch Intern Med. 1998;158:2054-62. [PMID: 0009778206]

8. **Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM.** Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med. 1999;341:217-25. [PMID: 0010413733]

9. **Robinson K, Conroy RM, Mulcahy R, Hickey N.** The 15-year prognosis of a first acute coronary episode in women. Eur Heart J. 1992;13:67-9. [PMID: 0001577034]

10. **Johansson S, Bergstrand R, Ulvenstam G, Vedin A, Wilhelmsson C, Wedel H, et al.** Sex differences in preinfarction characteristics and longterm survival among patients with myocardial infarction. Am J Epidemiol. 1984;119:610-23. [PMID: 0006711549]

11. **Peter T, Harper R, Luxton M, Penington C, Sloman JG.** Acute myocardial infarction in women. The influence of age on complications and mortality. Med J Aust. 1978;1:189-91. [PMID: 0000651740]

12. **Udvarhelyi IS, Gatsonis C, Epstein AM, Pashos CL, Newhouse JP, McNeil BJ.** Acute myocardial infarction in the Medicare population. Process of care and clinical outcomes. JAMA. 1992;268:2530-6. [PMID: 0001404820]

13. **Pohjola S, Siltanen P, Romo M.** Five-year survival of 728 patients after myocardial infarction. A community study. Br Heart J. 1980;43:176-83. [PMID: 0007362710]

14. **Wong ND, Cupples LA, Ostfeld AM, Levy D, Kannel WB.** Risk factors for long-term coronary prognosis after initial myocardial infarction: the Framingham Study. Am J Epidemiol. 1989;130:469-80. [PMID: 0002763992]

15. **Weinblatt E, Shapiro S, Frank CW.** Prognosis of women with newly diagnosed coronary heart disease—a comparison with course of disease among men. Am J Public Health. 1973;63:577-93. [PMID: 0004716368]

16. **Goldberg RJ, Gorak EJ, Yarzebski J, Hosmer DW Jr, Dalen P, Gore JM, et al.** A communitywide perspective of sex differences and temporal trends in the incidence and survival rates after acute myocardial infarction and out-of-hospital deaths caused by coronary heart disease. Circulation. 1993;87:1947-53. [PMID: 0008504508]

17. **Fiebach NH, Viscoli CM, Horwitz RI.** Differences between women and men in survival after myocardial infarction. Biology or methodology? JAMA. 1990;263:1092-6. [PMID: 0002299781]

18. **Vaccarino V, Krumholz HM, Mendes de Leon CF, Holford TR, Seeman TE, Horwitz RI, et al.** Sex differences in survival after myocardial infarction in older adults: a community-based approach. J Am Geriatr Soc. 1996;44:1174-82. [PMID: 0008855995]

19. **Orencia A, Bailey K, Yawn BP, Kottke TE.** Effect of gender on long-term outcome of angina pectoris and myocardial infarction/sudden unexpected death. JAMA. 1993;269:2392-7. [PMID: 0008479065]

20. **White HD, Barbash GI, Modan M, Simes J, Diaz R, Hampton JR, et al.** After correcting for worse baseline characteristics, women treated with thrombolytic therapy for acute myocardial infarction have the same mortality and morbidity as men except for a higher incidence of hemorrhagic stroke. The Investigators of the International Tissue Plasminogen Activator/Streptokinase Mortality Study. Circulation. 1993;88:2097-103. [PMID: 0008222103]

21. **Liao Y, Cooper RS, Ghali JK, Szocka A.** Survival rates with coronary artery disease for black women compared with black men. JAMA. 1992;268:1867-71. [PMID: 0001285782]

22. **Kostis JB, Wilson AC, O'Dowd K, Gregory P, Chelton S, Cosgrove NM, et al.** Sex differences in the management and long-term outcome of acute myocardial infarction. A statewide study. MIDAS Study Group. Myocardial Infarction Data Acquisition System. Circulation. 1994;90:1715-30. [PMID: 0007923655]

23. **Goldberg RJ, Gore JM, Alpert JS, Dalen JE.** Recent changes in attack and survival rates of acute myocardial infarction (1975 through 1981). The Worcester Heart Attack Study. JAMA. 1986;255:2774-9. [PMID: 0003701991]

24. **Goldberg RJ, Gore JM, Alpert JS, Dalen JE.** Incidence and case fatality rates of acute myocardial infarction (1975-1984): the Worcester Heart Attack Study. Am Heart J. 1988;115:761-7. [PMID: 0003354404]

25. **Pagley PR, Yarzebski J, Goldberg R, Chen Z, Chiriboga D, Dalen P, et al.** Gender differences in the treatment of patients with acute myocardial infarction. A multihospital, community-based perspective. Arch Intern Med. 1993;153:625-9. [PMID: 0008439225]

26. **Chiriboga DE, Yarzebski J, Goldberg RJ, Chen Z, Gurwitz J, Gore JM, et al.** A community-wide perspective of gender differences and temporal trends in the use of diagnostic and revascularization procedures for acute myocardial infarction. Am J Cardiol. 1993;71:268-73. [PMID: 0008427166]

27. **Goldberg RJ, Yarzebski J, Lessard D, Gore JM.** A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective. J Am Coll Cardiol. 1999;33:1533-9. [PMID: 0010334419]

28. **Cox DR.** Regression models and life tables. Journal of the Royal Statistical Society. 1972;74:187-220.

29. **Abbott RD, Donahue RP, Kannel WB, Wilson PW.** The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. JAMA. 1988;260:3456-60. [PMID: 0002974889]

30. **Donahue RP, Goldberg RJ, Chen Z, Gore JM, Alpert JS.** The influence of sex and diabetes mellitus on survival following acute myocardial infarction: a community-wide perspective. J Clin Epidemiol. 1993;46:245-52. [PMID: 0008455049]

31. **Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, et al.** Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care. 1998;21:69-75. [PMID: 0009538972]

32. **Behar S, Boyko V, Reicher-Reiss H, Goldbourt U.** Ten-year survival after acute myocardial infarction: comparison of patients with and without diabetes. SPRINT Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial. Am Heart J. 1997;133:290-6. [PMID: 0009060796]

33. **Flanders WD, Rhodes PH.** Large sample confidence intervals for regression standardized risks, risk ratios, and risk differences. J Chronic Dis. 1987;40:697-704. [PMID: 0003597672]

34. **Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM.** Impact of history of diabetes mellitus on hospital mortality in men and women with first acute myocardial infarction. The National Registry of Myocardial Infarction 2 Participants. Am J Cardiol. 2000;85:1486-9; A7. [PMID: 0010856398]

35. **Lerner DJ, Kannel WB.** Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J. 1986;111:383-90. [PMID: 0003946178]

36. **Coronado BE, Griffith JL, Beshansky JR, Selker HP.** Hospital mortality in women and men with acute cardiac ischemia: a prospective multicenter study. J Am Coll Cardiol. 1997;29:1490-6. [PMID: 0009180109]

37. **Hochman JS, McCabe CH, Stone PH, Becker RC, Cannon CP, DeFeo-Fraulini T, et al.** Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. TIMI Investigators. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol. 1997;30:141-8. [PMID: 0009207635]

38. **Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, et al.** Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. N Engl J Med. 1999; 341:226-32. [PMID: 0010413734]

39. **Cunningham MA, Lee TH, Cook EF, Brand DA, Rouan GW, Weisberg MC, et al.** The effect of gender on the probability of myocardial infarction among emergency department patients with acute chest pain: a report from the Multicenter Chest Pain Study Group. J Gen Intern Med. 1989;4:392-8. [PMID: 0002677270]

40. **Maynard C, Litwin PE, Martin JS, Weaver WD.** Gender differences in the treatment and outcome of acute myocardial infarction. Results from the Myocardial Infarction Triage and Intervention Registry. Arch Intern Med. 1992;152: 972-6. [PMID: 0001580724]

41. **Robinson K, Conroy RM, Mulcahy R, Hickey N.** Risk factors and in-hospital course of first episode of myocardial infarction or acute coronary insufficiency in women. J Am Coll Cardiol. 1988;11:932-6. [PMID: 0003356838]

42. **Krumholz HM, Douglas PS, Lauer MS, Pasternak RC.** Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? Ann Intern Med. 1992;116:785-90. [PMID: 0001567092]

43. **Albert CM, McGovern BA, Newell JB, Ruskin JN.** Sex differences in cardiac arrest survivors. Circulation. 1996;93:1170-6. [PMID: 0008653838]

44. **Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R.** Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation. 1998;97:2110-6. [PMID: 0009626170]

45. **Wexler LF.** Studies of acute coronary syndromes in women—lessons for everyone [Editorial]. N Engl J Med. 1999;341:275-6. [PMID: 0010413741]

46. **Losordo DW, Kearney M, Kim EA, Jekanowski J, Isner JM.** Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. Circulation. 1994;89:1501-10. [PMID: 0008149515]

47. **Hanke H, Hanke S, Ickrath O, Lange K, Bruck B, Muck AO, et al.** Estradiol concentrations in premenopausal women with coronary heart disease. Coron Artery Dis. 1997;8:511-5. [PMID: 0009431479]

48. **La Vecchia C, Decarli A, Franceschi S, Gentile A, Negri E, Parazzini F.** Menstrual and reproductive factors and the risk of myocardial infarction in women under fifty-five years of age. Am J Obstet Gynecol. 1987;157:1108-12. [PMID: 0003688065]

49. **Oliver MF.** Ischaemic heart disease in young women. Br Med J. 1974;4: 253-9. [PMID: 0004425852]

50. **Punnonen R, Jokela H, Aine R, Teisala K, Salomaki A, Uppa H.** Impaired ovarian function and risk factors for atherosclerosis in premenopausal women. Maturitas. 1997;27:231-8. [PMID: 0009288695]

51. **Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, et al.** Age at natural menopause and risk of cardiovascular disease. Arch Intern Med. 1999;159:1061-6. [PMID: 0010335682]

52. **Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH.** Menopause and the risk of coronary heart disease in women. N Engl J Med. 1987;316:1105-10. [PMID: 0003574358]

53. **Carney RM, Rich MW, Freedland KE, Saini J, teVelde A, Simeone C, et al.** Major depressive disorder predicts cardiac events in patients with coronary artery disease. Psychosom Med. 1988;50:627-33. [PMID: 0002976950]

54. **Frasure-Smith N, Lesperance F, Talajic M.** Depression following myocardial infarction. Impact on 6-month survival. JAMA. 1993;270:1819-25. [PMID: 0008411525]

55. **Case RB, Moss AJ, Case N, McDermott M, Eberly S.** Living alone after myocardial infarction. Impact on prognosis. JAMA. 1992;267:515-9. [PMID: 0001729573]

56. **Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS.** Psychosocial influences on mortality after myocardial infarction. N Engl J Med. 1984;311: 552-9. [PMID: 0006749228]

57. **Berkman LF, Leo-Summers L, Horwitz RI.** Emotional support and survival after myocardial infarction. A prospective, population-based study of the elderly. Ann Intern Med. 1992;117:1003-9. [PMID: 0001443968]

58. **Weinblatt E, Ruberman W, Goldberg JD, Frank CW, Shapiro S, Chaudhary BS.** Relation of education to sudden death after myocardial infarction. N Engl J Med. 1978;299:60-5. [PMID: 0000661862]

59. **Williams RB, Barefoot JC, Califf RM, Haney TL, Saunders WB, Pryor DB, et al.** Prognostic importance of social and economic resources among medically treated patients with angiographically documented coronary artery disease. JAMA. 1992;267:520-4. [PMID: 0001729574]

60. **Gabbay FH, Krantz DS, Kop WJ, Hedges SM, Klein J, Gottdiener JS, et al.** Triggers of myocardial ischemia during daily life in patients with coronary artery disease: physical and mental activities, anger and smoking. J Am Coll Cardiol. 1996;27:585-92. [PMID: 0008606268]

61. **Rozanski A, Bairey CN, Krantz DS, Friedman J, Resser KJ, Morell M, et al.** Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease. N Engl J Med. 1988;318:1005-12. [PMID: 0003352695]

62. **Rahe RH, Romo M, Bennett L, Siltanen P.** Recent life changes, myocardial infarction, and abrupt coronary death. Studies in Helsinki. Arch Intern Med. 1974;133:221-8. [PMID: 0004812746]

63. **Rozanski A, Blumenthal JA, Kaplan J.** Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation. 1999;99:2192-217. [PMID: 0010217662]

64. **Rosen M, Spetz CL, Hammar N.** Coronary artery disease in men and women [Letter]. N Engl J Med. 1999;341:1931-2. [PMID: 0010610473]