Sex-Based Analysis of Outcome in Patients With Acute Myocardial Infarction Treated Predominantly With Percutaneous Coronary Intervention

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Context A higher mortality risk for women with acute myocardial infarction (AMI) is a common finding in studies that compare the postinfarction outcome of women vs men. It is not clear, however, whether sex is an independent predictor of death among patients systematically treated with aggressive reperfusion and medical strategies.

Objective To assess the impact of patient's sex on outcome in a consecutive series of patients with AMI treated with a reperfusion strategy largely based on percutaneous coronary interventions.

Design, Setting, and Patients Inception cohort of 1937 patients (502 women and 1435 men) who were admitted with a diagnosis of AMI to a tertiary referral institution between January 1995 and December 2000.

Main Outcome Measures Mortality at 1 year after AMI.

Results Compared with men, women were older (70 vs 61 years; $P<.001$) and had known diabetes or hypertension more often. Both men and women received essentially identical therapy with the majority of patients (86%) receiving reperfusion therapy via percutaneous coronary interventions. There were no significant differences in 1-year Kaplan-Meier death rates with 13.8% (68 cases) among women and 12.9% (184 cases) among men (unadjusted hazard ratio, 1.06; 95% confidence interval, 0.80-1.39; $P=.70$). After age adjustment, women had a lower risk of death (hazard ratio, 0.65; 95% confidence interval, 0.49-0.87; $P=.004$).

Conclusion Despite their more advanced age and greater prevalence of diabetes or hypertension, women with AMI who were treated with a reperfusion strategy largely based on percutaneous coronary interventions show a similar outcome as men.

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In the last 20 years, cardiovascular disease has caused more deaths among women than among men.[1] Furthermore, from 1979 through 1998, mortality from cardiovascular diseases in the United States has steadily decreased in men but has remained relatively constant and even increased in women.[1]

Acute myocardial infarction (AMI) is the major cardiovascular cause of death in men and women. A considerable number of studies have focused on sex-related differences in outcome in patients with this disease. Prevailing evidence supports that short- and long-term mortality is higher in women than in men.[2] Less intense use of both pharmacological and device-based therapies, biological factors, older age, and more severe cardiovascular risk profiles have been used to explain higher mortality rates among women.[3] Important limitations of previous studies have included restriction to selected subsets suitable for thrombolysis[4-10] and the inclusion of cohorts of patients in whom reperfusion strategies were used relatively infrequently.[11-20]

Randomized studies performed in the past few years have demonstrated that percutaneous coronary interventions (PCIs) are more effective reperfusion strategies than intravenous thrombolysis.[21,22] Outcomes of primary PCI in patients with AMI have improved further with the use of the glycoprotein IIb/IIIa inhibitors.[23-25] However, PCI is still used less frequently than thrombolysis in patients with AMI.[26] Data on differences in outcome between women and men with AMI treated with PCI are limited and have been restricted to selected subsets of patients.[27,28] However, an important secondary analysis of a randomized study suggested that a difference in outcome in favor of men

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was found only after thrombolysis and not after PCI.[29]

The objective of the present study was to assess the impact of female sex on the outcome of a consecutive series of patients with MI treated with an aggressive reperfusion strategy largely based on PCI.

METHODS

Patients

This study included all 1937 patients who were admitted to the Deutsches Herzzentrum and 1. Medizinische Klinik rechts der Isar in the period between January 1995 and December 2000 with a diagnosis of AMI. The diagnosis of AMI was based on the presence of at least 1 episode of chest pain within the last 48 hours lasting 20 minutes or longer combined with either typical electrocardiographic changes (≥0.1 mV of ST-segment elevation in ≥2 limb leads or ≥2 mV in ≥2 contiguous precordial leads, presumed new complete left bundle-branch block) or increase of creatine kinase and its mb isoenzyme twice above the upper limit of normal. All of these patients were followed up according to a prospectively defined protocol to which they had given their informed consent.

The decision about which treatment approach to use was made by the responsible physician. Primary PCI was the preferred approach and the use of thrombolysis was mostly dictated by enrollment in randomized clinical trials (78% of the cases treated with thrombolysis). During the entire study period, a continuous on-call service was operative around the clock to provide the patients with AMI the option of a prompt PCI.

The collection of hospital data and performance of 30-day, 6-month, and 1-year clinical follow-up in patients with AMI for research purposes was approved by the institutional ethics committee.

Definitions and Follow-up Protocol

The main outcome measure was all-cause mortality. Other outcomes of interest were recurrent nonfatal MI and stroke. Diagnosis of recurrent infarction was based on typical chest pain, new ST-segment changes, and an increase in creatine kinase of at least 50% over the previous trough level in at least 2 samples reaching 240 U/L or higher. The diagnosis of stroke required confirmation by computed tomography or magnetic resonance imaging of the head. During the hospital stay, creatine kinase and its isoenzyme were determined immediately after admission and at least daily thereafter. After discharge, the assessment of clinical status was made by means of a telephone interview at 30 days, a follow-up visit at 6 months or whenever dictated by patient complaints, and a telephone interview at 1 year. Only 3.0% of men and 2.9% of women were lost to follow-up.

Table 1. Patient Demographics, Cardiovascular Risk Profile, and Infarct Characteristics*

Variable	Women (n = 502)	Men (n = 1435)	*P* Value
Age, y†	70.3 [60.8, 83.0]	60.7 [52.4, 70.0]	<.001
Arterial hypertension‡	366 (72.9)	875 (61.0)	<.001
Diabetes	127 (25.3)	258 (18.0)	<.001
Receiving insulin therapy	52 (10.4)	63 (4.4)	<.001
Current smoker	130 (25.9)	619 (43.1)	<.001
Cholesterol level, mg/dL†§	200 [173, 240]	199 [170, 234]	.12
Prior myocardial infarction	82 (16.3)	317 (22.1)	.001
Prior CABG surgery	17 (3.4)	87 (6.1)	.02
Prior PCI	38 (7.6)	154 (10.7)	.04
Anterior myocardial infarction	235 (46.8)	611 (42.6)	.09
ST-segment elevation on the admission electrocardiogram	322 (64.1)	931 (64.9)	.77
Killip class			
I	333 (66.3)	973 (67.8)	.33
II	84 (16.7)	232 (16.2)	
III	25 (5.0)	51 (3.6)	
IV	60 (12.0)	179 (12.4)	
Systolic blood pressure, mm Hg†	125 [110, 140]	120 [110, 140]	.40
Diastolic blood pressure, mm Hg†	70 [60, 80]	70 [60, 80]	.69
Heart rate, beats/min†	81 [70, 94]	80 [70, 90]	.005
Time to admission, h†	7.5 [3.0, 16.8]	6.3 [2.5, 15.0]	.02

*Values are presented as number (percentage) unless otherwise indicated. CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention.
†Data are presented as median [25th, 75th percentiles].
‡Defined as a systolic blood pressure of 140 mm Hg or greater and/or a diastolic blood pressure of 90 mm Hg or greater on at least 2 separate occasions.
§To convert to mmol/L, multiply by 0.0259.

Statistical Analysis

Differences between men and women were assessed using a 2-sided χ^2 or Fisher exact test for categorical data as appropriate, and the Wilcoxon rank sum test for continuous data. Survival curves were constructed by the Kaplan-Meier method with differences in survival assessed with the log-rank test. Multivariable analyses were performed by using Cox proportional models after confirming the validity of the proportional hazards assumption by the Therneau function.[30] We formerly assessed the interaction between sex and age with respect to mortality. Potential confounders were entered into models if they showed univariable differences between women and men with a $P<.10$. All statistical analyses were performed using S-Plus Version 4.5 software (Mathsoft Inc, Seattle, Wash). All *P* values are 2-tailed. A *P* value of less than .05 was considered significant.

RESULTS

Patient Demographics and Cardiovascular Risk Profile

Baseline characteristics according to sex are listed in TABLE 1. Women were older and were also more likely to have

Table 2. Procedures, Primary Treatment, and Concomitant Drug Therapy*

Variable	Women (n = 502)	Men (n = 1435)	*P* Value
Emergency coronary angiography	438 (87.3)	1270 (88.5)	.46
Primary PCI	426 (84.9)	1237 (86.2)	.46
Primary intravenous thrombolysis†	48 (9.6)	143 (10.0)	.79
Emergency CABG surgery	7 (1.4)	26 (1.8)	.53
Administration of abciximab	334 (66.5)	919 (64.0)	.31
Concomitant drug therapy			
Aspirin	454 (90.4)	1309 (91.2)	.60
β-Blockers	433 (86.3)	1242 (86.6)	.87
ACE inhibitors	421 (83.9)	1221 (85.1)	.51
Nitrates	52 (10.4)	125 (8.7)	.27
Calcium-channel blockers	15 (3.0)	39 (2.7)	.75
Statins	387 (77.1)	1147 (79.9)	.18

*Data are presented as number (percentage). PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft; and ACE, angiotensin-converting enzyme.
†The thrombolytic agent used was alteplase.

Table 3. Major Complications Within 30 Days After Admission*

	Women (n = 502)	Men (n = 1435)	*P* Value
Death	42 (8.4)	122 (8.5)	.93
Nonfatal recurrent myocardial infarction	3 (0.6)	21 (1.5)	.13
Nonfatal stroke	2 (0.4)	1 (0.1)	.33
Any of the above events	47 (9.4)	144 (10.0)	.66

*Values are presented as number (percentage).

systemic arterial hypertension and diabetes. Smoking was encountered less frequently among women. They were also less likely to have a history of previous MI, bypass surgery, or PCI.

Infarct Characteristics

Infarct characteristics according to sex are also listed in Table 1. Compared with men, women presented at the hospital with a longer delay from onset of symptoms and tended to have a higher frequency of anterior infarction. However, among patients who received thrombolysis or PCI, there was no difference in the time interval from admission to treatment between women (median, 95 minutes; interquartile range, 70 and 150 minutes) and men (median, 95 minutes; interquartile range, 61 and 150 minutes) ($P=.33$). Killip class distributions were also similar.

Procedures, Primary Treatment, and Concomitant Drug Therapy

Treatment characteristics according to sex are shown in TABLE 2. Coronary angiography was performed in an extensive and comparable proportion of men and women. Reperfusion therapy was instituted in an essentially identical proportion of women and men and PCI was the predominant strategy (applied in 86% of patients). Two thirds of the patients also received the glycoprotein IIb/IIIa inhibitor abciximab as part of reperfusion treatment. After primary treatment, men and women were treated frequently with β-blockers, angiotensin-converting enzyme inhibitors, and statins in similar proportions.

Clinical Outcome

The 30-day event rates are shown in TABLE 3. No significant differences between women and men were evident. In addition, revascularization of the infarct-related artery was required in 6.2% of the women and 7.2% of the men ($P=.48$) within the first 30 days after the primary treatment. In the small group of patients who did not receive reperfusion therapy, 32% of whom were in Killip class III or IV, mortality rates during the first 30 days were 14.3% among women and 20.7% among men ($P=.56$).

Target vessel revascularization rates 1 year after initial treatment were 19.3% for women and 20.9% for men ($P=.45$).

Cumulative mortality curves are shown in FIGURE 1. There was no significant difference in 1-year Kaplan-Meier death rate (13.8% or 68 cases among women and 12.9% or 184 cases among men; unadjusted hazard ratio [HR] for 1-year mortality, 1.06; 95% confidence interval [CI], 0.80-1.39; $P=.70$).

We next focused on age-adjusted mortality according to sex because of the substantial age difference between women and men. Age was entered into the model as a nonlinear variable. After adjustment for age, female sex was associated with reduced mortality (HR, 0.65; 95% CI, 0.49-0.87; $P=.004$). FIGURE 2 shows the mortality risk of women and men as a function of age. No significant interaction was found between sex and age with respect to mortality. Age-adjusted analyses were performed for several prespecified subgroups (FIGURE 3). Women in these subgroups had a consistent reduction in age-adjusted risk (Figure 3).

We constructed a multivariable Cox model for 1-year mortality including all characteristics from Table 1 that differed with $P<.10$ between women and men (age, hypertension, diabetes, smoking, previous MI, prior coronary artery bypass graft, prior PCI, anterior MI, heart rate, and time to admission), as well as sex itself. Female sex was independently predictive of a lower mortality (HR, 0.67; 95% CI, 0.50-0.91; $P=.01$). The most powerful risk factor was older age, with an HR of 1.69 (95% CI, 1.50-1.89) for a 10-year increment. Other strong risk factors were a history of coronary artery bypass graft (HR, 2.41; 95% CI, 1.62-3.59) and diabetes (HR, 1.80; 95% CI, 1.38-2.36).

COMMENT

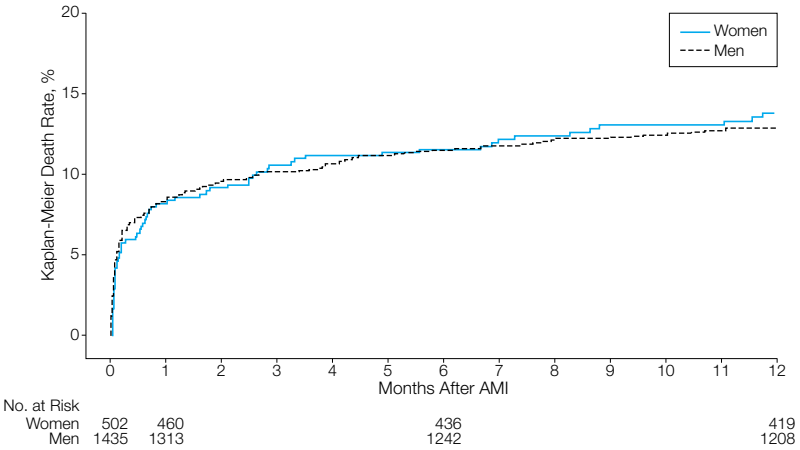
In this study, we included all 1937 patients who presented at our center for primary treatment of AMI during a 6-year period. To avoid bias, no selection criteria were applied regarding de-

mographic characteristics, clinical status at presentation, time interval from symptom onset, and treatment approach used. Twenty-six percent of the patients were women, about 90% of the patients had emergency coronary angiography, and 86% underwent primary PCI as a reperfusion strategy. Importantly, both women and men received essentially identical therapy with no sex-based difference in the use of PCI or evidence-based concomitant medical treatment (use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, etc). Considering the high proportion of patients treated with primary PCI, the results of this study should be regarded as representing what might be expected from a systematic interventional approach in the treatment of patients with AMI.

The main finding of this study indicates that women with AMI treated with this strategy had a prognosis similar to that of men, despite their significantly older age at presentation. This finding complements that of a previous study of ours including noninfarct patients with coronary stenoses treated with stenting[31]; together, these findings suggest that, in general, women with coronary artery disease benefit from emergency or elective PCI to at least the same degree as men.

A major strength of this study is the inclusion of an unselected and consecutive population of patients with AMI. This was achieved by including all the patients who sought primary treatment in our institution. In this regard, our study is similar to previous studies that included patients irrespective of the therapy received.[11,12,14,18-20] Other reports have been confined to selected populations with a specific reperfusion therapy.[4-8,32,33] In line with previous reports, women in this study differed from men in that they were older, more likely to have diabetes, arterial hypertension, anterior infarct localization, and they presented at the hospital with a greater delay from symptom onset. On the other hand, more male patients had a history of prior MI and coronary intervention. However, after adjusting for all these differences, women were found to have a significantly lower adjusted risk of death than men.

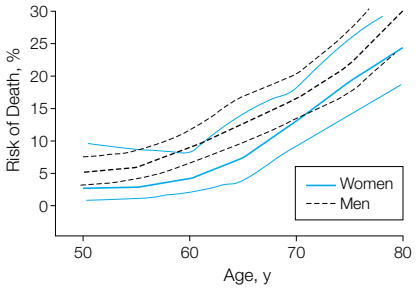
Figure 1. One-Year Cumulative Incidence of Death in Women and Men With Acute Myocardial Infarction (AMI)



We included all patients admitted during the period between 1995 and 2000. Accounting for the period in which the studies are performed is important for reducing the bias associated with recent treatment advances. We found a 30-day mortality rate of 8.4% in women and 8.5% in men. Based on the data from the National Registry of Myocardial Infarction 2 (collected between 1994 and 1998), Vaccarino et al[18] reported an in-hospital mortality rate of 16.7% and 11.5% among women and men, respectively. There are some important differences in patient characteristics between those study cohorts and ours. The patients included in the current study were slightly younger but more likely to present with cardiogenic shock.[18] A major difference was seen in the frequency and type of reperfusion treatment: less than 25% of the patients in the study by Vaccarino et al[18] received any reperfusion treatment, and most of those received thrombolysis.

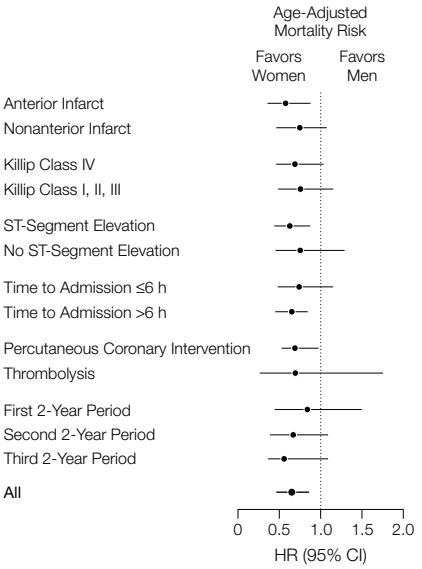
In a recent study by Gottlieb et al,[19] which included patients treated from 1992 to 1996, 30-day mortality rates were 17.6% among women and 9.6% among men. The patients in the latter study appear to be comparable with the patients in our study regarding age and other entry characteristics, yet reperfusion was attempted in only about 50% of the cases, mostly with thrombolysis.[19] A higher mortality rate for women with AMI has also been observed in population-based studies.[34] All of these reports[11,14,15,18,19] indicate that patients with AMI are at higher risk if no reperfusion therapy is applied. It is possible that women with AMI, who usually are older than men, might suffer greater disadvantages if no reperfusion treatment is provided. Although the life-saving role of thrombolysis as the most widely used option for reperfusion is well established,[35] many patients are not eligible for thrombolysis,[17] and these patients are at particularly high risk.[36] Therefore, the interventional strategy applied among

Figure 2. Risk of Death Among Women and Men With Acute Myocardial Infarction as a Function of Age



Curves were derived from Cox proportional hazards regression models including age as a nonlinear variable. Thin lines show the 95% confidence intervals.

Figure 3. Age-Adjusted Hazard Ratios (HRs) for Death During 1 Year After Admission in Various Subgroups



The HRs were obtained by using Cox proportional hazards regression models including sex and age as covariates. CI indicates confidence interval.

patients who did not meet conventional eligibility criteria for thrombolysis may have contributed to the reduction of the excess risk carried by women. In addition, the large use of glycoprotein IIb/IIIa inhibition has probably had a positive impact on the results of our study. Cho et al[37] found abciximab to be particularly beneficial in women undergoing coronary stenting.

An excess mortality risk among women has also been evidenced in secondary analyses of thrombolysis trials.[4-6] A comparison of absolute mortality rates observed in those trials and in the present study may be misleading because the thrombolysis trials generally included younger and hemodynamically stable patients. Also, while the thrombolysis trials have usually enrolled only patients with ST-segment elevation MI who presented early (<6-12 hours) after symptom onset, our study encompassed both patients with ST-segment elevation MI and those with non-ST-segment elevation MI, patients who presented early and those who presented after 12 hours from symptom onset. We used thrombolysis in a limited number of selected patients, which prevents us from drawing conclusions in this regard.

After 1 year, we could not detect any significant difference in mortality between women and men with AMI. In comparison with previous analog studies in patients with AMI,[16,19] the use of medications such as β-blockers, angiotensin-converting enzyme inhibitors, and statins was much more frequent in the present study. Based on previous evidence,[38-40] the intensive pharmacological therapy has probably influenced the overall results in this consecutive series, but we do not know whether women have had a greater benefit than men from this regimen.

Several limitations should be acknowledged before trying to draw conclusions from this study. First, it is a single-center study and the data presented need replication from other centers. Second, the relatively small sample size reduces the power of subset analyses and precluded the investigation of potentially important interactions. Third, these results may not be generalizable to centers that do not aggressively pursue a routine rapid reperfusion strategy mainly based on PCI. Finally, there were too few patients treated to determine whether similar results might have been seen had thrombolysis been the predominant treatment option.

We found that women with AMI treated with a reperfusion strategy largely based on PCI show a similar outcome with men, despite women's older age and more adverse risk profiles. Our results suggest that sex alone should not be a factor in deciding whether to perform primary PCI.

Author Contributions: *Study concept and design:* Kastrati, Dirschinger, Neumann, Schömig. *Acquisition of data:* Mehilli, Pache, Seyfarth, Blasini. *Analysis and interpretation of data:* Mehilli, Kastrati, Hall, Schömig. *Drafting of the manuscript:* Mehilli, Kastrati, Schömig. *Critical revision of the manuscript for important intellectual content:* Mehilli, Kastrati, Dirschinger, Pache, Seyfarth, Blasini, Hall, Neumann, Schömig. *Statistical expertise:* Mehilli, Kastrati. *Administrative, technical, or material support:* Dirschinger, Pache, Neumann, Schömig. *Study supervision:* Kastrati, Seyfarth, Blasini, Hall, Schömig.

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If there is no struggle there is no progress.
—Frederick Douglass (1817?-1895)