Sex Differences in Management and Outcome After Acute Myocardial Infarction in the 1990s

A Prospective Observational Community-Based Study

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Background—Previous studies have suggested that women with acute myocardial infarction (AMI) are less aggressively managed than are men. The aim of this study was to assess sex differences in medical and invasive coronary procedures (angiography, PTCA, and CABG) in AMI patients admitted to cardiac care units (CCUs) in Israel in the mid 1990s and their association with early and 1-year prognosis.

Methods and Results—We studied 2867 consecutive AMI patients (2125 men, 74%) hospitalized in all 25 CCUs in Israel from 3 prospective nationwide surveys conducted in 1992, 1994, and 1996. Women were, on average, older than men (69 versus 61 years, \( P < 0.0001 \)) and had a higher prevalence of hypertension, diabetes, Killip class II on admission, and in-hospital complications. Women received aspirin and \( \beta \)-blockers less often than did men, but these differences were not significant after age adjustment. The unadjusted rates of thrombolysis, angiography, and PTCA/CABG use were lower in women than in men but not after covariate adjustment: 42\% versus 48\% (adjusted odds ratio [OR] 0.92, 95\% CI 0.77 to 1.11), 23\% versus 31\% (OR 0.88, 95\% CI 0.70 to 1.09), and 15\% versus 19\% (OR 0.93, 95\% CI 0.72 to 1.19), respectively. The 30-day mortality was higher in women than in men (17.6\% versus 9.6\%, respectively; OR 1.39, 95\% CI 1.06 to 1.82), but the 30-day to 1-year mortality rate was not (9.1\% versus 5.6\%, respectively; hazard ratio 1.18, 95\% CI 0.84 to 1.66).

Conclusions—This prospective nationwide observational community-based study of consecutive AMI patients hospitalized in the CCUs in the mid 1990s indicates that women fare significantly worse than do men at 30 days but not thereafter at 1-year. The difference in 30-day outcome was not influenced by the use of different therapeutic modalities, including thrombolysis and invasive coronary procedures, but was rather due to the older age and greater comorbidity of women; these findings seem also to explain the less frequent use of invasive procedures in women. (Circulation. 2000;102:2484-2490.)

Key Words: myocardial infarction ■ sex ■ thrombolysis ■ angiography ■ revascularization ■ mortality

Previous studies have suggested differences in the application of specific therapeutic modalities in men compared with women with acute myocardial infarction (AMI). Some studies concentrating mainly on thrombolysis and invasive coronary procedures (angiography, PTCA, and CABG) found a less invasive approach in women than in men,\(^1\)-\(^5\) whereas others found no evidence for sex-related differences in the use of thrombolysis or invasive procedures.\(^6\)-\(^10\) Few studies evaluated sex differences in the use of pharmacological agents.\(^6\)

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It is commonly held that women have a worse prognosis early after AMI,\(^10\)-\(^14\) especially at younger ages (\( \leq 75 \) years).\(^15\) Most of the recent studies evaluated sex differences in outcome after AMI in selected populations of trials,\(^13\),\(^16\),\(^17\) whereas data comparing the management and outcome in unselected male and female patients in the 1990s are scarce.\(^15\)

In the present study, we assessed sex differences in the use of pharmacological agents, thrombolytic therapy, and invasive coronary procedures (angiography, PTCA, and CABG) in 3 prospective observational community-based studies of all AMI patients admitted to all coronary care units (CCUs) in Israel in the mid 1990s and their association with 30-day and 1-year prognoses.

Methods

Patients

The patients in this cohort were derived from 3 prospective nationwide surveys conducted during a 2-month period (January and
Results of continuous variables are reported as mean ± SD. The nonparametric Wilcoxon test was used to compare the time from pain onset to thrombolytic therapy in men and women. Two-sided probability values are reported.

In-hospital complications were compared between men and women, first without adjustment for any baseline characteristics and then with adjustment for age (SAS LOGISTIC Procedure), in terms of odds ratios (ORs) with 95% CIs. In-hospital management was compared between men and women, first without adjustment, then with adjustment for age alone, and finally with adjustment for age and other covariates by means of multivariate stepwise logistic regression analyses (SAS LOGISTIC Procedure). In each model tested, sex of the patient was forced into the model, whereas other predictors were selected in a stepwise manner.

Mortality in men and women was compared first without adjustment, then with adjustment for age alone, and finally with adjustment for age and other covariates, with and without the addition of medications (aspirin, β-blockers, and ACE inhibitors) and invasive coronary procedures. To compare 30-day mortality in men and women, in terms of OR (95% CI), stepwise logistic regression analysis was performed (SAS LOGISTIC Procedure). To compare first-year mortality in 30-day survivors and cumulative first-year mortality in men and women in terms of hazard ratio (HR, with 95% CI), stepwise Cox proportional-hazard regression models (SAS PHREG Procedure) were used.

Survival curves were estimated by the method of Kaplan-Meier. The significance of the difference between the survival curves was assessed by the log-rank test (SAS LIFETEST Procedure). Multivariate adjusted survival curves were constructed by use of the SAS PHREG Procedure.

Results

Clinical Characteristics

Clinical characteristics are shown in Table 1. Women were older than men, had greater comorbidity, and were more hemodynamically compromised on admission.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
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<tbody>
<tr>
<td>Women (n=742)</td>
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<tr>
<td>-----------------</td>
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<tr>
<td>Patients in cohort, %</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Range</td>
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<tr>
<td>&lt;55, n (%)</td>
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<tr>
<td>55–64, n (%)</td>
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<tr>
<td>65–74, n (%)</td>
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<tr>
<td>≥75, n (%)</td>
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<tr>
<td>Nationality</td>
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<tr>
<td>Arabs, n (%)</td>
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<tr>
<td>Patient history, n (%)</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Angina</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
</tr>
<tr>
<td>PTCA/CABG</td>
</tr>
<tr>
<td>On admission</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>Q-wave MI, n (%)</td>
</tr>
<tr>
<td>Anterior MI location, n (%)</td>
</tr>
<tr>
<td>Peak CK, IU</td>
</tr>
</tbody>
</table>

Values are mean±SD or as indicated. MI indicates myocardial infarction. Percentages reported were calculated without missing values. *By χ² test comparing women and men.

Complications

In-hospital complications (Table 2) were more frequent in women than in men, except for ventricular tachycardia and fibrillation, which were more frequent in men. Adjustment for age reduced the ORs for the differences between the sexes.

Management

In-hospital management is shown in Table 3. Women were less often treated with aspirin and β-blockers but more often treated with digitalis, differences that vanished after adjustment for age alone. Further adjustment for age and other covariates did not change these ORs significantly, indicating that most of the differences in their use were age-related. The frequency of ACE inhibitor use was similar for both sexes. However, after adjustment for age alone or for age and other covariates, their use was lower in women than in men.

Thrombolytic therapy was less frequently used in women than in men (Table 3), a difference that vanished after age adjustment or after adjustment for age and other covariates. The median time from pain onset to thrombolysis was slightly
longer in women than in men (3.7 versus 3.0 hours, respectively; $P=0.005$) as the result of a longer delay from pain to admission (2.2 versus 1.6 hours, respectively; $P<0.001$) but not from admission to treatment (1.2 versus 1.2 hours, respectively; $P=0.82$). Reasons for exclusion from thrombolytic therapy differed for men and women ($P=0.02$). In men ($n=1085$), the main reason was disqualifying ECG (41%), followed by late arrival (24%), contraindication (23%), and other reasons (12%), whereas in women ($n=421$), the main reasons were either disqualifying ECG (33%) or late arrival (30%), followed by contraindication (21%) and other reasons (15%).

Coronary arteriography and PTCA were performed less frequently in women than in men; these differences vanished after adjustment for age alone or after adjustment for age and other covariates (Table 3). Performance of CABG was infrequent for both sexes. Among catheterized patients, the rates of PTCA and/or CABG were similar in women (111 of 171, 65%) and men (411 of 656, 63%). Primary PTCA was rarely performed (2.3% of men and 0.9% of women, $P=0.02$). Insertion of pacemakers (4% versus 5% in men and women, respectively; $P=0.18$) and Swan-Ganz catheters (2% in men and women) were infrequent in both sexes.

### Mortality
Crude mortality rates at 30 days, 30 days to 1 year, and 1 year were significantly higher in women than in men (Table 4 and Figures 1A, 1B, and 2A) and increased significantly with advancing age in both sexes (Figures 1A and 1B). The unadjusted relative risks of dying in women compared with...
men declined markedly after adjustment for age alone (Table 4). Further adjustments for age and other covariates revealed similar results (Table 4). The covariate-adjusted risk of dying was significantly higher in women than in men at 30 days but not at 30 days to 1 year, and as a consequence, the cumulative 1-year mortality risk of dying in women relative to men was less evident (Figure 2B) but still existed (Table 4). Further adjustments for other covariates of treatment (thrombolysis, PTCA or CAGB, \(\beta\)-blockers, aspirin, and ACE inhibitors) revealed similar results (data not tabulated). There was no significant interaction between age and sex, and the risk of dying did not differ significantly in young and old women along the age subgroups tested (<55, 55 to 64, 65 to 74, and \(\geq\)75 years; Figure 1). Analysis of patients aged <80 years and of those with a first AMI showed results similar to those of the whole cohort.

There was a significant interaction between sex and AMI type (Q wave versus non–Q wave) for 30-day (\(P=0.02\)) and 1-year (\(P=0.01\)) mortality. Women with Q-wave AMI fare worse than do men at 30 days (21.7% versus 10.4%, respectively; adjusted OR 1.74, 95% CI 1.28 to 2.37) and at 1-year (29.0% versus 15.3%, respectively; HR 1.53, 95% CI 1.23 to 1.91). On the other hand, the mortality of women and men with non–Q-wave AMI was similar at 30 days (8.9% versus 7.1%, respectively; adjusted OR 0.78, 95% CI 0.42 to 1.40) and at 1-year (17.4% versus 12.8%; HR 0.87, 95% CI 0.59 to 1.29).

<table>
<thead>
<tr>
<th>Follow-Up Period</th>
<th>Women, (n (%))</th>
<th>Men, (n (%))</th>
<th>(P^*)</th>
<th>Unadjusted RR (95% CI)</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Covariate-Adjusted RR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d</td>
<td>131/742 (17.6)</td>
<td>203/2124 (9.6)</td>
<td>&lt;0.0001</td>
<td>2.03 (1.60–2.57)</td>
<td>1.40 (1.09–1.79)</td>
<td>1.39 (1.06–1.82)</td>
</tr>
<tr>
<td>30 d to 1 y</td>
<td>55/605 (9.1)</td>
<td>106/1900 (5.6)</td>
<td>0.002</td>
<td>1.63 (1.19–2.23)</td>
<td>1.14 (0.81–1.58)</td>
<td>1.18 (0.84–1.66)</td>
</tr>
<tr>
<td>Cumulative 1 y</td>
<td>186/736 (25.3)</td>
<td>309/2103 (14.7)</td>
<td>&lt;0.0001</td>
<td>1.72 (1.46–2.02)</td>
<td>1.29 (1.06–1.56)</td>
<td>1.28 (1.06–1.56)</td>
</tr>
</tbody>
</table>

Relative risk (RR) is OR for 30-d mortality and hazard ratio for 1-y mortality for 30-d survivors and for cumulative 1-y mortality in women vs men.

*Unadjusted, by \(\chi^2\) test, comparing women and men.

†By multivariate stepwise analyses adjusting for age, hypertension, diabetes, prior MI, Killip class II on admission, Q-wave MI, and anterior infarct location (see Methods).

**Figure 1.** Thirty-day and 1-year crude mortality rates by age subgroups in men (A) and women (B). \(P\) for trend <0.0001 for both 30-day mortality and incremental 1-year mortality rates in both sexes.

**Figure 2.** Cumulative 1-year survival curves for men and women. A, Unadjusted Kaplan-Meier curves. \(P=0.0001\) (log-rank test) for sex differences. B, Adjusted survival curves predicted from Cox model.
Discussion
This prospective observational community-based study of consecutive AMI patients of all ages hospitalized in all CCUs in Israel in the mid 1990s demonstrates that women fare significantly worse than do men at 30 days but not thereafter at 1-year. Women, on average, were older and had greater comorbidity than did men. Although a seemingly lower use in women than in men of β-blockers, aspirin, thrombolysis, and invasive coronary procedures was noted, after age adjustment, the medical and the invasive management of AMI in both sexes was similar. Our results indicate that sex alone does not influence the use of different therapeutic modalities and that differences in outcome were not affected by the use of different therapies, including thrombolysis and PTCA or CABG, but rather by the women’s older age and the presence of more unfavorable prognostic factors and comorbidity.

In-Hospital Complications
In accordance with other studies, women had more mechanical complications (congestive heart failure, shock, and acute mitral regurgitation6–8,10–17,19–23), electrical complications (advanced heart block and asystole15,20,24,25 and paroxysmal atrial fibrillation17,20,24), and stroke6,15,17 than did men. Most of these complications remained more common in women even after age adjustment (Table 2). The reduction in the ORs obtained after age adjustment indicates that, in part, the older age of women contributed to the sex differences in complication rates. In accordance with earlier studies, life-threatening ventricular arrhythmias were less common in women than in men,5,10,15,20 whereas advanced heart block and asystole were more common.15,20,24,25 These findings are possibly explained by greater vagal activation in women than in men after an abrupt coronary occlusion, which may protect against arrhythmia.26

In-Hospital Management
In accordance with previous reports, women were less likely to be treated with aspirin6,15 and β-blockers5,15 but more likely to be treated with digitalis.6–22 However, after age or covariate adjustments, the medical management was similar, in accordance with other findings,6 except for ACE inhibitors, which, after adjusting for age alone, were used significantly less in women than in men. It seems that because of the greater use of ACE inhibitors at older ages (30% for <65 years versus 39% for ≥65 years, \(P<0.0001\)), adjustment for age unmasks the sex difference in their use.

Several earlier studies noted that women were less likely to receive thrombolysis even after adjustment for ineligibility due to older age, comorbid conditions, and late arrival.4,27,28 In the present study, the difference in thrombolysis use disappeared after adjustment for age alone. Similar to earlier reports, the time from pain onset to arrival was longer in women, which may explain the delay in administering thrombolysis in women10,16,17,23 and the higher proportion of women excluded from thrombolytic therapy because of late arrival.5

Women underwent less coronary angiography and revascularization than did men, a difference that disappeared after age adjustment. These findings are in accordance with studies reporting similar rates of these procedures in men and women7–10,21,29 but in discordance with others.1,3–5,15 Furthermore, once angiography was performed, there were no sex-related differences in the use of PTCA and/or CABG (65% and 63% of catheterized women and men, respectively), in accordance with most earlier reports.2,4,21,30

The differences in invasive procedure rates in the various reports may be related, in part, to the study populations tested. In our survey, all consecutive AMI patients hospitalized in CCUs were included, whereas others studied first AMIs with an age limitation,10 patients with discharge diagnosis of AMI,7 selected and nonconsecutive AMI patients participating in a clinical trial,2,8,9,23 or patients with a statewide abstracted discharge diagnosis of AMI.1,5 Moreover, differences among states and countries in patient characteristics and management,31 as well as differences between hospitals in the same country,32 may account for the diverging results.

Mortality
Previous reports suggested that less aggressive management of AMI in women may explain some of their excess mortality.1,5 In the present study, after age adjustment, women fare worse only at 30 days but not thereafter. Adjustments for other baseline covariates with and without treatments (thrombolysis, PTCA or CABG, β-blockers, aspirin, and ACE inhibitor) did not change the mortality risk of women. Furthermore, inasmuch as after age adjustment, no differences were observed in the management of men and women, most of the difference in mortality seems to be age-related and not associated with differences in therapy.

In accordance with most previous studies and reviews,11,14,16,17,19 an increased crude mortality in women during the early phase after AMI was found. Adjustments for age and/or clinical characteristics decreased the magnitude of the relative risk of women to men but did not eliminate it. On the other hand, after the early phase, only a few studies reported an increased crude mortality in women, and when adjustments were made for age and other baseline characteristics, the prognosis for women did not differ from that for men.13,12,14,17,33 and in some studies, women fared even better.11,14,19

In a recent publication from the National Registry of Myocardial Infarction-2 (NRMI-2), Vaccarino et al15 noted an increased in-hospital mortality among women compared with men aged 30 to 89 years (16.7% versus 11.5%, respectively). Sex-based differences in mortality varied according to age. Among patients aged <50 years, the mortality among women was more than twice that of men. The difference in the rates decreased with increasing age and was no longer significant after the age of 74 (\(P<0.001\) for interaction between sex and age). The present study is in discordance with that large study on several points but in accordance with the findings of others.16 In the present study, no significant interaction was observed between age and sex, and the risk of dying did not differ significantly in young and old women compared with men along the age subgroups tested. Also, the proportion of women in the present study and in most cohorts published was much smaller (26%) than that in the NRMI-2 (40%), whereas the frequency of thrombolytic, β-blocker,
and ACE inhibitor use was higher in our cohort. Our results are in accordance with a recent study by Hochman et al., who showed a significant interaction between sex and AMI type (Q wave versus non-Q wave). Thus, only women with Q-wave AMI fare worse than do men at 30 days and 1 year, whereas the outcome of women and men with non-Q-wave AMI was similar.

Study Limitations
The present study included only patients with AMI who were hospitalized in the CCUs but not patients dead on arrival or those who died in the emergency room or who were admitted to the general ward. Because the decision to admit patients with AMI to the CUC was not directed by a national policy but rather was left to the discretion of each center and to bed availability, we cannot exclude the possibility, described by others, that older patients (a group that included more women) were admitted to the ward. The more advanced age of women, concomitant medical illnesses, longer time from symptom onset to hospitalization, atypical presentation of AMI symptoms, and nonspecific ECG changes, might have reduced the probability of being admitted to a CUC and of receiving thrombolytics or undergoing invasive coronary procedures, which are usually initiated in the CUC setting.

In all 3 surveys (in 1992, 1994, and 1996), our registry was performed in January and February to eliminate the effect of potential seasonal variations. We do not have information regarding the incidence of mortality rates during other months, and we cannot exclude a seasonal variation as well, with lower mortality rates in nonwinter months. It is conceivable that if such seasonal variation exists, it will affect mortality of both sexes similarly, as noted by others. However, during periods with lower incidence of AMI, the availability of performing an angiogram or PTCA/CABG may increase and may include more patients who at other seasons could have been excluded from such procedures (ie, the elderly, women, and patients with comorbidities).

Conclusions
This prospective observational community-based study of unselected AMI patients hospitalized in the CCUs in the mid 1990s, including those who did not receive thrombolytics, indicates a higher mortality in women at 30 days but not thereafter. This difference in outcome was not associated with a difference in the use of therapeutic modalities, including thrombolyis and invasive coronary procedures, but rather with the older age and greater comorbidity of women. The lower use of invasive procedures in women relates also to their older age and higher comorbidity rate.

Acknowledgments
We are indebted to all physicians and nurses who participated in the Israeli Thrombolytic Surveys in 1992, 1994, and 1996. We are grateful to Dalia Ben-David for the data collection and to Mark Goldberg for programming the database.

References


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