Sex-Based Differences in Early Mortality of Patients Undergoing Primary Angioplasty for First Acute Myocardial Infarction

Babak A. Vakili, MD; Robert C. Kaplan, PhD; David L. Brown, MD

Background—Morbidity and mortality after an acute myocardial infarction (AMI) has been reported to be higher in women than men. However, in some prior reports, women were not treated as aggressively as men, suggesting a treatment bias. We sought to determine whether sex influenced short-term outcomes in a cohort of AMI patients, all of whom underwent primary angioplasty.

Methods and Results—We conducted a retrospective cohort study of all patients undergoing primary angioplasty for a first AMI in New York State in 1995. A total of 1044 patients, 317 women and 727 men, were identified. Mean age was 59±12 years in men and 65±12 years in women (P<0.05). Women had a higher prevalence of hypertension (59% versus 44%, P<0.05), diabetes (19% versus 14%, P<0.05), and peripheral vascular or carotid disease (9.5% versus 5.5%, P<0.05) than men. Men were more likely to be treated earlier (within 6 hours) from the time of symptom onset than women (74% versus 63%, P<0.05). Women had a higher incidence of shock or hemodynamic instability than men (25% versus 17%, P<0.05). The unadjusted in-hospital mortality rate was 7.9% in women and 2.3% in men (P<0.05). After multivariate logistic regression analysis, women maintained a 2.3-fold higher risk of in-hospital death compared with their male counterparts (95% confidence interval [CI], 1.2 to 4.6, P=0.016).

Conclusions—After correcting for age and baseline risk differences, women undergoing primary angioplasty for AMI have a significantly higher in-hospital mortality rate than men. (Circulation. 2001;104:3034-3038.)

Key Words: sex • myocardial infarction • survival • angioplasty
information on the hospital and cardiologist, patient demographics, procedural information, risk factors, discharge status, vessels diseased, lesion location and morphology, presence of bypass grafts, pre- and post-procedural stenosis, and complications. The DOH is the coordinating center, and hospitals and their catheterization laboratories are responsible for the accurate documentation and transfer of data. The DOH conducts periodic site visits to check for the accuracy of data entry, and errors and discrepancies are brought to the attention of each laboratory to be rectified.

The 1995 New York State Coronary Angioplasty Registry includes >22,000 patients undergoing elective and emergent PTCA in 32 hospitals. The time from symptom onset to treatment is recorded as <6 hours, 6 to 23 hours, or the number of days. Because significant numbers of patients with AMI present >6 hours from symptom onset and late presentation may be associated with worse outcome, we included patients who underwent attempted PTCA for AMI within 23 hours of symptom onset. This definition of primary PTCA is consistent with that used by the Society of Cardiac Angiography and Interventions. We excluded patients with a prior AMI to examine the biological response to AMI in a population experiencing first AMI. We also excluded patients who had been treated with thrombolytic therapy within the previous 7 days or those with prior open-heart surgery. To determine the population from which the current study cohort was derived, we queried the New York State 1995 Statewide Planning and Research Cooperative System (SPARCS) database for all patients admitted to a hospital with a principal diagnosis of AMI (ICD-CM-9 code 410.xx).

Statistical Analysis
Categorical variables were compared by χ² analysis. Continuous variables are presented as mean±SD and were compared using Student’s t test. All probability values are 2-tailed. Statistical significance was defined as P<0.05 or CIs that did not include 1.0. Forward multiple logistic regression models were developed to identify predictors of in-hospital mortality. The model was constructed to determine the relation between sex and mortality among patients with AMI treated with PTCA. Variables sequentially added to the model included age, medical history, time to treatment, and hemodynamic status. The reference group consisted of male patients. Model discrimination was assessed by use of area under the receiver operating characteristic curve. A potential interaction between age and sex was examined using multivariate logistic regression, with age stratified at 75 years or with a linear age variable. All analyses were performed using the SPSS 8.0 statistical analysis program.

Missing Data
Baseline demographics, comorbidities, and procedure and outcome data were recorded in every case. However, ejection fraction values were missing for 30% of women and 33% of men. Logistic regression was performed both by excluding patients with missing values and by imputing an ejection fraction using the mean ejection fraction of patients according to sex. Women were older than men (65 versus 59 years, P<0.005) and were more likely to have hypertension (59% versus 44%, P=0.005), diabetes (19% versus 14%, P=0.036), and peripheral or cerebrovascular disease (9.5% versus 5.5%, P=0.019). Race, body mass index, and history of current smoking did not differ between sexes. Men were more often treated earlier than women (74% versus 63% treated within 6 hours of symptom onset, P<0.001).

Angiographic characteristics of patients are depicted in Table 2. Left ventricular ejection fraction was not significantly different between women and men (47% versus 48%, P=NS). The mortality rate for men with missing ejection fractions was 2.9%, compared with a mortality rate of 2.1% for men without missing values (P=0.49). The mortality rate of women with missing ejection fractions was 10.4%, compared with a mortality of 6.8%.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women (n=317)</th>
<th>Men (n=727)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>47±14</td>
<td>48±12</td>
<td>NS</td>
</tr>
<tr>
<td>Missing values, %</td>
<td>30</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Vessels diseased, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>59</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Left main disease</td>
<td>1.6</td>
<td>0.7</td>
<td>NS</td>
</tr>
<tr>
<td>LAD disease</td>
<td>63</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Left circumflex disease</td>
<td>36</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>RCA disease</td>
<td>51</td>
<td>53</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD or percent of patients. LV indicates left ventricular; LAD, left anterior descending coronary artery; RCA, right coronary artery; and NS, not significant.
for women without missing values \((P=0.27)\). There were no significant differences in number or distribution of diseased coronary vessels between women and men, including 3-vessel (12% versus 15%, \(P=\text{NS}\)) and left main coronary disease (1.6% versus 0.7% \(P=\text{NS}\)).

Procedural characteristics are shown in Table 3. The annual PTCA experience of the treating physicians and hospitals did not differ between men and women. Before the procedure, significantly more women than men were either in shock (systolic blood pressure \(<80\text{ mm Hg}\) or cardiac index \(<2.0\text{ L min}^{-1}\text{ m}^{-2}\)) or required pharmacological or mechanical support to maintain blood pressure or cardiac output (25% versus 17%, \(P=0.003\)). The use of balloon angioplasty, stent placement, and atherectomy was similar in women and men. A successful angioplasty result, defined by a reduction of treated vessel stenosis of at least 20% and a final diameter stenosis \(<50\%\), was achieved in 98% of women and 99% of men \((P=\text{NS})\). Procedural complications, including stroke, abrupt closure, renal failure requiring dialysis, vascular complications, and emergency coronary bypass surgery were low and not significantly different between women and men.

The unadjusted in-hospital mortality rate was 7.9% in women and 2.3% in men \((P<0.005;\text{Table 4})\). The unadjusted odds ratio for death for women compared with men was 3.58 (95% CI, 1.9 to 6.7). Of note, the mortality of those \(<75\text{ years of age}\) was 1.6% among men and 5.5% among women \((P=0.001)\). The mortality of women \(\geq 75\text{ years of age}\) was 14.6%, compared with 8.4% among older men \((P=0.212)\). Multivariate logistic regression analysis using either age of 75 as a discrete cut point or age as a linear variable did not reveal a significant age-sex interaction. Women who presented for treatment \(<6\text{ hours after symptom onset}\) had a mortality of 8.5% compared with 2.4% among men who were treated early \((P<0.001)\). Treatment from 6 to 23 hours after symptom onset resulted in a mortality rate of 6.8% among women and 2.1% for men \((P=0.037)\). Within each sex, there was no significant difference in mortality between patients treated early or late.

After adjusting for baseline characteristics, including age, hypertension, diabetes, peripheral vascular or carotid disease, shock or hemodynamic instability, and time to treatment by multivariable logistic regression analysis, the odds ratio for in-hospital death for women remained significantly elevated at 2.33 (95% CI, 1.2 to 4.6, \(P=0.016)\). For the final model, the area under the receiver operating characteristic curve was 0.87, which is consistent with excellent model discrimination \((\text{Table 4})\).

### Discussion

The present study confirmed the plethora of previous studies that have demonstrated an increase in in-hospital mortality of women compared with men presenting with AMI.\(^2-20\) As in some, but not all, prior studies,\(^3,15-20\) the increased risk of mortality persisted after correction for age and other medical conditions. The persistence of a survival disadvantage after risk-adjustment in prior studies may have been due to a lower rate of use of established treatments, such as aspirin,\(^19\) \(\beta\)-blockers,\(^17,19\) thrombolytic treatment,\(^18\) cardiac catheterization,\(^18,30,36\) PTCA,\(^30\) and bypass surgery\(^30\) in women. A strength of the current study is its uniform application of primary angioplasty to all patients, thereby eliminating possible mortality differences caused by less aggressive treatment of women. Thus, the unique finding of the current study is that after adjusting for age, medical conditions, time to treatment, and hemodynamic status in patients uniformly

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**TABLE 3. Procedural Characteristics of Women and Men Undergoing Primary PTCA for AMI**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women (n=317)</th>
<th>Men (n=727)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operator annual PTCA volume (\geq75) cases, %</td>
<td>89.4</td>
<td>89.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital annual PTCA volume (\geq400) cases, %</td>
<td>88.0</td>
<td>88.3</td>
<td>NS</td>
</tr>
<tr>
<td>Shock or hemodynamic instability, %</td>
<td>25</td>
<td>17</td>
<td>0.003</td>
</tr>
<tr>
<td>Revascularization modality, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>97</td>
<td>97</td>
<td>NS</td>
</tr>
<tr>
<td>Stent</td>
<td>16</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Atherectomy</td>
<td>4.9</td>
<td>3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Angiographic success (\geq1) lesion, %</td>
<td>98</td>
<td>99</td>
<td>NS</td>
</tr>
<tr>
<td>Procedural complications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.9</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Abrupt closure</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.6</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Emergency CABG surgery</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
</tbody>
</table>

CABG indicates coronary bypass graft; NS, not significant.

OR denotes odds ratio; CI, confidence interval; and ROC, receiver operating characteristic. Men served as the reference group. Medical history includes diabetes, hypertension, and peripheral or cerebrovascular vascular disease. Hemodynamic status includes shock, requirement for vasopressors, or intra-aortic balloon counterpulsation.

\(|P|<0.001; \|P|<0.006; \|P|<0.003; \|P|<0.016\).

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**TABLE 4. In-Hospital Mortality and Odds Ratios for Death Among Women and Men Undergoing Primary Angioplasty for AMI**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=317)</th>
<th>Men (n=727)</th>
<th>ROC Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>7.9%</td>
<td>2.3%</td>
<td>...</td>
</tr>
<tr>
<td>Unadjusted OR (95% CI)</td>
<td>3.58 (1.9–6.7)*</td>
<td>1.00</td>
<td>0.65</td>
</tr>
<tr>
<td>OR adjusted for age (95% CI)</td>
<td>2.47 (1.3–4.7)†</td>
<td>1.00</td>
<td>0.77</td>
</tr>
<tr>
<td>OR adjusted for age and medical history (95% CI)</td>
<td>2.69 (1.4–5.2)‡</td>
<td>1.00</td>
<td>0.80</td>
</tr>
<tr>
<td>OR adjusted for age, medical history, time to treatment, and hemodynamic status (95% CI)</td>
<td>2.33 (1.2–4.6)§</td>
<td>1.00</td>
<td>0.87</td>
</tr>
</tbody>
</table>
treated with primary PTCA for AMI, women retained a 2.3-fold increased risk of death during their admission. It is of considerable importance to understand why, in a cohort of patients all receiving the same aggressive treatment, women continue to fare worse than men.

Role of Age
A recent analysis of the Cooperative Cardiovascular Project data demonstrated a 24% increase in the risk of 30-day mortality among women compared with men presenting with AMI. However, after adjustment for confounders such as age, preexisting conditions, illness severity, and treatment differences, no mortality difference remained. Of note, in this study, which was comprised exclusively of Medicare recipients, the mean age for women and men was 78.0 and 75.2 years, respectively. Other studies of elderly patients have also tended not to find sex-based differences in mortality. However, studies that exclude elderly patients generally show higher mortality rates among women, even after adjustment for baseline differences, suggesting an age-sex interaction. A recent analysis of the National Registry of Myocardial Infarction 2 data set found that the excess risk of mortality for women was accentuated at earlier ages and tended to disappear in older patients. Although data from the current study show similar trends, the number of patients may not have been adequate to demonstrate a statistically significant age-sex interaction.

Time to Treatment
Women with AMI generally present to the hospital later than men. A longer time from symptom onset to presentation to the hospital has been associated with greater mortality in trials of thrombolytic therapy. It remains undetermined whether late treatment increases mortality among patients treated with primary angioplasty. In the current study, later treatment did not increase mortality among women or men.

Response to Treatment
In contrast to studies of thrombolytic therapy for AMI in which women seem to experience reocclusion, hemorrhagic complications, and strokes more often than their male counterparts, in this primary angioplasty study, the procedural success and complication rates were equal for men and women. Thus, rather than a differential response to treatment, our findings suggest that fundamental differences exist between the biology and pathophysiology of AMI among relatively younger men and women.

Biology
Estrogen seems to protect women against the development of coronary atherosclerosis. Thus, when relatively young women develop an AMI after the rupture of vulnerable plaque, they have less severe coronary stenoses than older women or men. Because of the relative paucity of advanced coronary stenoses before their infarction, women may not have previously generated an ischemic response capable of protecting the myocardium during infarction by triggering preconditioning and/or the development of collateral blood supply. Sex-related differences in myocardial physiology and compliance may also contribute to higher mortality among women. This study and others have observed that despite similar left ventricular systolic function, women have a higher prevalence of shock and hypotension after AMI than men. Whether more severe diastolic dysfunction accounts for the hemodynamic instability is not known. Other possible mechanisms for the worse outcome among women include sex-related differences in autonomic function after ischemia. Women have been shown to have an accentuated vagal response, with more frequent bradycardia and hypotension in the setting of ischemia compared with men.

Implications
Until sex-specific treatments are developed to narrow the mortality difference between men and women, educational resources should applied to reinforce the role of primary prevention and stress the earlier recognition of the frequently atypical symptoms of ischemia and infarction in women. Given the greater prevalence of adverse clinical characteristics and the associated increase in mortality among women, women should perhaps be referred more frequently rather than less often than men for aggressive, invasive therapy.

Limitations
Several important limitations need to be borne in mind when interpreting this study. First, because of its nonrandomized, retrospective nature, there may remain significant unrecognized differences between men and women, even after correction for the observed differences. However, unlike randomized trials, the current study included high-risk patients typically excluded from clinical trials, including those with advanced age and shock. Second, this data set does not include information on the treatment of patients with aspirin, ß-blockers and ACE inhibitors, all of which have been shown to reduce mortality in the setting of AMI. It is possible that the undertreatment of women with these agents contributed to their increased mortality. Third, only in-hospital outcomes are analyzed in the current study. Although it is possible that the survival advantage for men would dissipate with extended follow-up, most deaths after AMI occur in the hospital. Fourth, significant selection biases for primary angioplasty treatment exist for both men and women. It is possible that more women than men with high-risk characteristics not included in the database are referred for primary angioplasty. Finally, it is possible that women have a worse outcome in the hospital because they survive to be admitted to the hospital, whereas the sicker men die before they arrive at the hospital. The data in this area are unclear and worthy of further investigation.

Conclusion
The persistence of a survival disadvantage for women undergoing the same aggressive treatment as men after adjustment for age, other comorbid conditions, time to treatment, and hemodynamic status suggests the possibility of basic biological differences in the response to AMI between men and women.
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