Sex Differences in Hospital Mortality After Coronary Artery Bypass Surgery
Evidence for a Higher Mortality in Younger Women

Viola Vaccarino, MD, PhD; Jerome L. Abramson, PhD; Emir Veledar, PhD; William S. Weintraub, MD

Background—Data are conflicting over whether women have higher mortality than men after coronary artery bypass graft (CABG) surgery. Younger but not older women hospitalized for acute myocardial infarction have higher in-hospital mortality rates than men. We hypothesized that younger women also have higher in-hospital mortality rates after CABG.

Methods and Results—We studied 51,187 patients (30% women) included in the National Cardiovascular Network database who received CABG at 23 clinical centers between October 1993 and December 1999. Compared with men, fewer women were white and more women had risk factors and comorbidities. These differences were more apparent in younger patients. In all age groups, however, women had higher left ventricular ejection fraction and fewer diseased vessels. Women had higher in-hospital mortality rates than men, but sex differences in mortality were more marked among younger patients. Women <50 years of age were 3 times more likely to die than men (3.4% versus 1.1%), and women 50 to 59 years of age were 2.4 times more likely to die than men (2.6% versus 1.1%). In the older age categories, the sex difference in in-hospital mortality was less marked (P<0.001 for the interaction between sex and age). Adjustment for preoperative risk factors only slightly decreased the strength of this interaction.

Conclusions—Younger women undergoing CABG surgery are at a higher risk of in-hospital death than men, but this difference in risk decreases with advancing age. Additional investigation is needed to determine why in-hospital mortality is higher in women after CABG, with particular focus on younger women. (Circulation. 2002;105:1176-1181.)

Key Words: sex ▪ mortality ▪ bypass

Coronary artery bypass graft (CABG) surgery has been shown to be an effective method for treating angina pectoris and prolonging life in patients with severe coronary artery disease. The number of women patients undergoing CABG surgery is increasing. In 1998, there were ~550,000 CABG procedures performed in the United States, of which 28%, or ~150,000, were performed on women. However, it has not yet been determined whether women benefit from this procedure to the same extent as men. Major randomized trials of the efficacy of CABG surgery compared with medical therapy have either included only men3-5 or have predominantly included men. Furthermore, observational studies comparing outcomes between women and men after CABG surgery have provided conflicting results as to whether or not sex is an independent predictor of death, especially in the early postoperative period.5-16

Younger women with myocardial infarction (MI) represent a high-risk group compared with men. Studies have shown that younger women with a MI have higher in-hospital, 30-day, and postdischarge mortality. We anticipated that this patient group might also be at risk for adverse outcomes after CABG.

The purpose of this study was to investigate whether younger, but not older, women have a greater risk of in-hospital death after CABG surgery than men of similar age and whether presently known risk factors and comorbidity would explain such mortality differences. The National Cardiovascular Network (NCN), a large contemporary database of CABG procedures across the United States, provided an excellent resource to examine these questions.

Methods

Study Population

Details of the methods and variable definitions used in the NCN database have been reported. Information on patient characteristics, post-CABG complications, and in-hospital mortality was collected by trained personnel at each hospital site and submitted to the NCN data coordinating center between October 1993 and

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December 1999. Hospitals that did not provide information on in-hospital mortality or for which such information was incomplete in specific years were not included in our database. Of 55 175 patients, 3988 (7%) were excluded because of missing data on sex or age, leaving 51 187 patients from 23 participating hospitals (listed in the appendix). Overall, the patients with missing data had similar clinical characteristics compared with the patients included in the analysis, thereby suggesting that these exclusions did not introduce substantial bias.

Data Analysis
First, we examined the distribution of patient characteristics according to sex in the entire group and within 10-year age subgroups. Next, we compared the in-hospital mortality rates between women and men according to 5 age groups (age <50, 50 to 59, 60 to 69, 70 to 79, and ≥80 years), and we used the Breslow-Day test to assess whether there was a significant interaction between sex and age. We then used a series of logistic regression models to assess the effect of groups of variables on the association of interest (sex and its interaction with age). In these models, age and its interaction with sex were used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for the in-hospital mortality of women versus men according to age group.

### TABLE 1. Distribution of Study Variables by Sex, in the Entire Sample and According to Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage of All Patients</th>
<th>OR (Women vs Men) for Characteristic, According to Age Group, *y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=36 009)</td>
<td>Women (n=15 178)</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>50–59</td>
</tr>
<tr>
<td>White</td>
<td>93.4</td>
<td>91.0</td>
</tr>
<tr>
<td>Height ≥170 cm</td>
<td>80.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Weight ≥80 kg</td>
<td>66.2</td>
<td>29.9</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>37.8</td>
<td>34.1</td>
</tr>
<tr>
<td>History of stroke</td>
<td>14.8</td>
<td>18.6</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>16.5</td>
<td>23.6</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>27.3</td>
<td>37.7</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>62.7</td>
<td>73.8</td>
</tr>
<tr>
<td>History of CABG</td>
<td>9.7</td>
<td>6.2</td>
</tr>
<tr>
<td>Angina class III or IV†</td>
<td>74.8</td>
<td>78.5</td>
</tr>
<tr>
<td>3-Vessel disease</td>
<td>63.7</td>
<td>58.5</td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≥40%</td>
<td>77.0</td>
<td>81.6</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Nonselective CABG</td>
<td>27.5</td>
<td>30.2</td>
</tr>
<tr>
<td>CABG+valve surgery</td>
<td>8.2</td>
<td>12.3</td>
</tr>
</tbody>
</table>

*P values are not presented because virtually all associations were statistically significant because of the large sample size.

†Canadian Cardiovascular Society Heart classification of angina.

Results
Of the 51 187 patients included in this study, 15 178 (29.7%) were women and 36 009 (70.3%) were men. The average age was 67.5 (±10.7) years for women and 64.1 (±10.7) years for men. As expected, women were smaller and weighed less than men (Table 1). Compared with men of similar age, younger women were less often white and had more comorbid conditions and risk factors, including stroke, heart failure, diabetes, renal insufficiency, and concomitant valve surgery, and they presented in higher angina class. These differences also included the priority of the CABG procedure (elective versus nonelective) and whether a valve procedure (repair or replacement) was performed in addition to the CABG. In the adjusted model, height, weight, angina class, number of diseased vessels, and ejection fraction were treated as continuous variables.

In an attempt to clarify causes of in-hospital death, we also examined the frequency of major postsurgery complications by age and sex. These included bleeding requiring reoperation, postoperative MI, neurological complications (stroke, transient ischemic attack, or coma), and renal failure.21 Although complete data on age, sex, and in-hospital mortality were available, some patients had missing data on other study factors. Missing data ranged from 1.5% persons with missing data on the procedure priority to 21.4% with missing data on angina class. To minimize bias resulting from the exclusion of patients with missing data, we used multiple imputation to fill in missing values. The imputation procedure was based on a method of simultaneous attribution and transformation of predictor variables, which uses the concepts of maximum generalized variance and canonical variables.22 Multiple imputation cannot completely remove the bias that might arise from missing covariable data, but it can help to reduce such bias. This technique appropriately adjusts standard errors in accordance with the uncertainty surrounding the imputed data.
became less marked in the older patients (Table 1). In all age groups, women had less severe coronary artery disease and higher left ventricular ejection fraction and had less often a prior history of MI or CABG compared with men.

Of the 15,178 women undergoing CABG, 804 (5.3%) died in hospital, whereas of the 36,009 men, 1036 (2.9%) died in hospital. In relative terms, women were substantially more likely than men to die at younger ages (Figure). In the youngest age category (<50 years old), the in-hospital death rate was about 3 times higher for women compared with men (3.4% versus 1.1%), and in the second youngest age category, women were 2.4 times more likely to die than men (2.6% versus 1.1%). The sex-based differences in in-hospital mortality tended to decrease with increasing age (P for interaction <0.001 by Breslow-Day test). Among the oldest patients (≥80 years), the in-hospital death rate was, in relative terms, only slightly higher in women compared with men (9.0% versus 8.3%).

In a logistic regression model that included sex, age, and the interaction between the 2 without adjusting for other patient characteristics (Table 2), the results were similar, as reported above. After adjusting for other patient characteristics, the interaction was somewhat attenuated but still substantial and highly significant, as shown in Table 2. In the adjusted model, women <50 years of age were more than twice as likely to die as men in this age bracket. In patients between 50 and 60 years of age, women experienced an 86% higher risk of in-hospital death than men. Sex differences in in-hospital mortality were less marked in the older-age subgroups.

An analysis of major postoperative complications by sex and age revealed that with the exception of bleeding requiring reoperation, women tended to suffer more complications after CABG than did men (Table 3). The sex differences in complications, in particular renal failure, neurological complications, and acute MI, were more marked at younger ages, particularly renal failure.

**Discussion**

In this large, multi-institutional cardiac surgery database, women patients tended to have a higher in-hospital mortality than men in all age groups. However, the risk was considerably higher among younger women and was only partially accounted for by differences in presenting characteristics and risk factors.

Previous studies examining sex differences in mortality after CABG surgery have produced a host of different results. Although most studies have documented a higher in-hospital or postoperative mortality in women compared with men, several investigators have concluded that when adjustment was made for differences in body size and clinical and angiographic variables, sex was not a predictor. In contrast, other studies have continued to document a higher mortality in women that persisted in multivariable analysis. However, these studies have typically not examined results stratified by age.

To our knowledge, only 3 studies have presented mortality data in men and women after age stratification. Consistent with our findings, all 3 of these studies have shown a
clear variation in the sex effect according to age. Gardner et al\textsuperscript{14} plotted in-hospital mortality rates by age and sex in patients receiving CABG between 1974 and 1983 at the Johns Hopkins Hospital. Their graph shows a markedly high mortality rate for women in the younger age groups, both in absolute terms and compared with men, especially among patients <50 years of age. In a recent report from the Society of Thoracic Surgery National Database,\textsuperscript{15} 30-day mortality rates were about 3 times higher in women than in men among patients <50 years, about 2 times higher in patients between 50 and 70 years, and only 40% higher in patients older than 70 years of age. Similarly, in a Swedish study focusing on long-term outcomes,\textsuperscript{25} female sex was associated with a relative risk of 2.1 for 5-year mortality among patients younger than 65 years, whereas among patients 65 years or older, the relative risk was 1.0. It should be noted that these results of greater mortality rate in younger women compared with men were incidental in these studies and were not adjusted for baseline differences.

**Possible Mechanisms**

In our study, younger women undergoing CABG had more comorbid conditions and risk factors compared with men, including stroke, heart failure, diabetes, renal insufficiency, and valve disease, and they presented in higher angina class. These differences became less marked in the older patients. The markedly higher prevalence of diabetes in the younger female patients compared with male patients is particularly noteworthy. Younger women had a distinctly higher risk of postoperative renal failure compared with men, and they also had higher rates of neurological complications and acute MI after the procedure. We had initially anticipated that the higher prevalence of comorbid conditions, in particular diabetes, would be responsible, to some extent, for the higher rates of in-hospital complications and death of younger women. However, when preexisting conditions and risk factors were accounted for in our multivariable model, they explained <30% of the mortality difference between women and men at younger age. Increased in-hospital mortality would also be expected with greater severity of coronary artery disease. However, we observed that women had less severe coronary artery disease and better left ventricular ejection fraction than men in all age categories, including younger women. Therefore, the reasons for the higher in-hospital mortality of younger women after CABG compared with men must involve alternative mechanisms.

Although the present study is the first, to our knowledge, to examine specifically whether younger women have a higher in-hospital mortality risk after CABG surgery than men, a similar question has been addressed in previous studies of patients hospitalized for MI. We\textsuperscript{17,19} and other investigators\textsuperscript{18} have demonstrated that young and middle-aged female patients have a remarkably higher in-hospital mortality risk than men after MI, even after accounting for comorbid conditions, cardiovascular risk factors, and clinical severity. In contrast, no sex differences in survival rates or even a better survival for women were found among MI patients of older age. As we had anticipated, our findings of in-hospital mortality after CABG closely parallel outcomes of patients hospitalized for MI.

Researchers have proposed that women with premature coronary artery disease have unknown risk factors or lack protective factors normally present in women.\textsuperscript{26} In efforts to determine mechanisms underlying the higher in-hospital mortality of younger women with MI, genetic and hormonal pathways have been hypothesized, including abnormalities of the estrogen receptor,\textsuperscript{27} ovarian dysfunction,\textsuperscript{28,29} premature menopause,\textsuperscript{30} and proinflammatory properties of hormone replacement therapy.\textsuperscript{31} Although it has been shown that estrogen has numerous protective effects on the cardiovascular system,\textsuperscript{32} a proinflammatory effect of exogenous hormone therapy has been described.\textsuperscript{33} The latter could cause unstable atherosclerotic plaques or a hypercoagulable state in women undergoing CABG. However, we found that women <50 years of age were the group with the highest in-hospital mortality compared with men. Thus, it seems unlikely that hormone replacement therapy plays a role, although it is possible that endogenous estrogen has similar proinflammatory effects.

An alternative explanation of our findings is a possible ascertainment bias. Because coronary heart disease in younger women, especially those <50 years of age, is comparatively rare, only the most severe cases may be recognized and treated.\textsuperscript{18} A referral bias might also play a role if women with symptoms of coronary heart disease are being referred less often or later than men.\textsuperscript{34} Consequently, only women with more severe coronary disease may receive CABG surgery. The fact that women more often had an acute presentation (urgent or emergent) and had a more severe angina class at the time of CABG does suggest potential sex
differences in diagnosis or referral, as reported in earlier studies. However, if the latter were true, one would also expect that the women would also have had more advanced coronary artery disease than men. This was not the case in our population. As noted above, we determined that women actually had less extensive coronary artery disease than men, a common observation in previous studies as well.

Another explanation for the higher in-hospital mortality of younger women may be that the smaller size of coronary arteries in women could increase the likelihood of perioperative and postoperative complications. The fact that in our study sex differences persisted after adjustment for measures of body size may not rule out this possibility, because women have smaller coronary arteries than men independent of body size. However, it remains difficult to explain why coronary artery anatomy would have a larger impact on in-hospital mortality in younger than in older women.

Limitations
As with other studies using large national cardiovascular registries, our analysis has limitations inherent to voluntary participation of individual centers. It is possible that centers with higher rates of operative complications and mortality failed to provide complete reports. However, in the NCN, patient outcomes were not released outside each institution, thereby encouraging honest reporting of outcomes. In addition, if this underreporting existed in the NCN, it is unlikely to have occurred differentially by sex, and, therefore, it should not affect our results. Another limitation is that the data available for analysis are those commonly recorded in the medical records. We did not have information on socioeconomic variables, reproductive history, menopausal status, or behavioral and psychosocial characteristics. Lacking such data, we were unable to determine whether these factors could play a role in the mortality differences we observed. Despite these limitations, however, this study does have the advantage of including many patients from a wide range of institutions in the United States, thereby allowing the study of specific subgroups, such as the younger patients, and enhancing the generalizability of the findings.

Conclusions
Younger women represent a high-risk group for in-hospital complications and mortality after CABG surgery compared with men. In view of our findings, additional investigation is needed to determine why in-hospital mortality is higher in women after CABG, with particular attention focused on younger women.

Appendix
NCN Participating Centers that contributed data for this report are Abbott-Northwestern, Minneapolis, Minn; Albany Medical Center, Albany, NY; Baptist Hospital, Birmingham, Ala; Bryan Memorial Hospital, Lincoln, Neb; Christ Hospital, Cincinnati, Ohio; Duke University Medical Center, Durham, NC; EHS Good Samaritan, Downers Grove, Ill; Emory Heart Center, Atlanta, Ga; Florida Hospital Medical Center, Orlando, Fla; Hillcrest Medical Center, Tulsa, Okla; Indiana Heart Institute, Indianapolis, Ind; Jewish Hospital, Louisville, Ky; Maine Medical Center, Portland, Me; Methodist Heart Institute, Memphis, Tenn; Mid-America Heart Institute, Kansas City, Mo; Shadyside Hospital, Pittsburgh, Pa; Sinai Hospital, Baltimore, Md; St Dominic’s Hospital, Jackson, Miss; St John’s Hospital, Springfield, Ill; St Luke’s Medical Center, Milwaukee, Wisc; St Vincent Infirmary, Little Rock, Ark; Washington Heart Center, Washington, DC; and William Beaumont Hospital, Royal Oak, Mich.
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