Differences Between Men and Women in Hospital Mortality Associated With Coronary Artery Bypass Graft Surgery

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Background. A prospective study of patients undergoing coronary artery bypass graft surgery (CABG) was conducted to examine differences in hospital mortality by sex. Outcome data on 3055 CABG patients undergoing operation between 1987 and 1989 were examined for differences in patient, disease, and treatment factors.

Methods and Results. Odds ratios (OR), risk differences, and 95% confidence intervals (CI95%) were calculated. Mortality rates for women (7.1%) and men (3.3%) differed, the OR (women vs men) being 2.23 (CI95%, 1.58 to 3.15). Women were older, more often diabetic, and had more urgent or emergent surgery; adjustment yielded an OR (women vs men) of 1.75 (CI95%, 1.17 to 2.63). Body surface area (BSA) was associated with risk of death in both sexes (P=.007) and positively associated with coronary artery luminal diameters. After adjustment for BSA, sex was no longer significantly associated with mortality (OR [women versus men] of 1.18; CI95%, 0.72 to 1.95). Internal mammary artery (IMA) grafting was performed less frequently among women than men (64.8% versus 78.4%, P<.001). Smaller BSA and absence of IMA grafting were each associated with increased risk of death (RD) from heart failure. Risk of death from heart failure (RD [women minus men] = 0.63; CI95%, 0.13 to 1.13) was greater among women; these accounted for 71.1% of the sex-specific difference in mortality rates.

Conclusions. Excess risk of hospital mortality among women having CABG was largely the consequence of death from heart failure and, to a lesser extent, from hemorrhage. Smaller BSA (probably because of its association with coronary artery luminal diameter) and the absence of IMA grafting were each associated with increased risk of death from heart failure. (Circulation. 1993;88[part 1]:2104-2110.)

Key words • sex • coronary disease • risk factors

A consistent finding among individuals undergoing coronary artery bypass graft surgery (CABG) is that women are at a higher risk of hospital mortality. As early as 1975, reports from four groups had demonstrated a higher risk of short-term mortality among women. Since 1975, these findings have been confirmed by 22 additional studies. These studies, which report outcomes on more than 120,000 CABGs, found hospital mortality more than twice as likely among women. This excess mortality has been variously attributed to more urgent or emergent CABG among women, greater technical difficulty in operating on women, and more severe coronary artery disease among women. Sex-related differences in diagnosis and treatment of coronary artery disease have also been described. Although many reports have noted a higher risk of mortality for women having CABG, only a few have systematically examined the underlying reasons for this difference.

Data collected on consecutive CABG procedures performed in northern New England provided an opportunity to determine differences in patient, disease, and treatment factors by sex and to examine the factors associated with the observed higher risk of hospital mortality among women.

Methods

All five medical centers and all 19 cardiothoracic surgeons in northern New England participated in this

*See "Appendix" for participating centers.

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*See "Appendix" for participating centers.
prospective cohort study. This study was approved by the Internal Review Boards of the participating institutions.

Patients undergoing CABG incidental to heart valve repair or replacement, resection of a ventricular aneurysm, or other surgical procedure were not included in this study. Hospital mortality was assessed, thus allowing for confirmation of rates using hospital discharge data.

Data were collected on the following variables: patient sex and age; Charlson comorbidity score; presence of unstable angina pectoris; prior CABG; cardiac catheterization results (ejection fraction [EF], left ventricular end-diastolic pressure [LVEDP], number of diseased coronary arteries, and the percentage stenosis of the left main coronary artery); preoperative use of intravenous nitroglycerin; preoperative placement of an intra-aortic balloon pump; priority of surgery (emergent, urgent, or elective); and status at hospital discharge (dead or alive). Medical records including death certificates for all deaths and autopsy records when available were reviewed to determine the primary cause of death.

Body surface area was calculated by the method of Dubois and Dubois:

$$\text{Body surface area} = \frac{\sqrt{\text{height (cm)} \times \text{weight (kg)}}}{3600}$$

Angiography reports were reviewed to assess the severity of coronary artery disease expressed as the number of diseased vessels. The EF results were scored by the method described by Pierpont et al (EF < 40%, 14; EF 40% to 49%, 12; EF 50% to 59%, 10; EF ≥ 60%, 6). Priority of surgery was assessed by the cardiothoracic surgeons using definitions previously described. Briefly, they are as follows: emergent, medical factors relating to the patient's cardiac disease dictate that surgery should be performed within hours to prevent morbidity or death; urgent, medical factors require the patient to stay in the hospital to have the operation before discharge; elective, medical factors indicate the need for operation, but the clinical picture allows discharge from the hospital with readmission at a later date. Discharge information, obtained from each hospital, was used to compile a comorbidity index using the method described by Charlson et al, Roos et al, and Roos and Roos. Luminal diameters of the coronary arteries at the site of the distal anastomosis were measured by cardiothoracic surgeons, with a set of graduated (1.0- to 3.5-mm) probes, on a series of 945 patients from one institution.

Data were collected on 3404 consecutive patients undergoing isolated CABG in Maine, New Hampshire, and Vermont between July 1, 1987, and April 15, 1989. Complete information on clinical variables, comorbidity, and outcome was available on 3055 patients. The mortality rate for the total number of cases (men, 3.2%; women, 6.8%) was virtually identical to the mortality rate in the analysis data set (men, 3.3%; women, 7.1%). Additional information on number of diseased coronary arteries was available for 2884 patients (94.4%).

Statistical Methods

Standard statistical methods were used for the calculation of odds ratios (OR), risk differences (RD), their 95% confidence intervals (CI95%), the $\chi^2$ test, and

In-hospital mortality stratified by age and sex (top) and by priority at surgery and sex (bottom).

Pearson's product moment correlation coefficient (r). RDs (also known as attributable risks) were calculated to contrast the cause-specific mortality rates of men and women. This allows the estimation of the absolute magnitude of the risk difference. Adjusted ORs were calculated for specific risk factors using logistic regression analysis. All $P$ values were two-tailed. Logistic regression analysis was used to assess the relation between patient, disease, and treatment characteristics and hospital mortality. For fixed-effects regression models, the analyses were performed with the SAS PROC LOGIST program; for random-effects models, the EGRET statistical package was used.

Results

Among the 3055 patients, there were 132 deaths (4.3%). The mortality rate was 3.3% for men (n=2236) and 7.1% for women (n=819). The mortality rate was higher for women in all age groups (see Figure). A larger percent of women had urgent (50.2% versus 39.2%) or emergent (8.2% versus 6.0%) surgery; women had higher rates of mortality for elective, urgent, and emergent surgery. Table 1 summarizes clinical, demographic, and treatment variables examined by sex and priority at surgery. Women were approximately 3 years older than men and had slightly higher Charlson comorbidity index scores, attributable primarily to
TABLE 1. Clinical, Demographic, and Treatment Variables Stratified by Sex and Priority at Surgery

<table>
<thead>
<tr>
<th>Clinical, Demographic, and Treatment Variables</th>
<th>Elective Surgery</th>
<th>Urgent/Emergent Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>n=1225 (54.8% of all men)</td>
<td>n=341 (41.6% of all women)</td>
</tr>
<tr>
<td>Age, y (mean)</td>
<td>61.4</td>
<td>64.3</td>
</tr>
<tr>
<td>Charlson comorbidity score (mean)</td>
<td>0.35</td>
<td>0.48</td>
</tr>
<tr>
<td>Peripheral vascular disease, % yes</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Diabetes, % yes</td>
<td>15.2</td>
<td>26.7</td>
</tr>
<tr>
<td>COPD, % yes</td>
<td>10.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Unstable angina, % yes</td>
<td>52.0</td>
<td>59.8</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft surgery, % yes</td>
<td>5.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Ejection fraction, % (mean)</td>
<td>57.6</td>
<td>59.9</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure, mm Hg (mean)</td>
<td>18.1</td>
<td>18.9</td>
</tr>
<tr>
<td>Poor cardiac function, % yes (EF &lt;40 and LVEDP &gt;20)</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Left main coronary artery stenosis ≥50%, % yes</td>
<td>14.7</td>
<td>11.7</td>
</tr>
<tr>
<td>Number of diseased coronary vessels (mean)</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Preoperative intravenous nitrroglycerin, % yes</td>
<td>3.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Preoperative intra-aortic balloon pump, % yes</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease; EF, ejection fraction; and LVEDP, left ventricular end-diastolic pressure.

higher rates of diabetes. Men more often had chronic obstructive pulmonary disease. Women also had a somewhat higher prevalence of unstable angina pectoris. Among urgent or emergent patients, men were approximately twice as likely to have had prior CABG. The mean EF was higher for women than men. The proportion of patients with poor cardiac function (ie, EF <40% and LVEDP >20 mm Hg) was similar for men and women. Angiographic data on the percent stenosis of the left main coronary artery was also very similar among men and women, as was the number of diseased coronary arteries. The mean number of distal anastomoses was 3.1 for men and 2.9 for women.

The crude OR (women versus men) for hospital mortality was 2.23 (CI95%, 1.58 to 3.15); adjustment for clinical, demographic, and treatment variables (listed in Table 1) yielded an adjusted OR (women versus men) of 1.75 (CI95%, 1.17 to 2.63).

Men had a significantly larger mean body surface area (mean±SEM: men, 1.99±0.04; women, 1.73±0.06; P<.001), and an inverse approximately quadratic relation between hospital mortality and body surface area was evident. An individual with a body surface area of <1.6 m² was approximately five times as likely to die as someone with a body surface area of ≥2.0 m² (Table 2), and this inverse relation was present in both sexes. Body surface area was independently associated with the risk of hospital mortality (OR [<1.6 vs ≥2.0 m²], 2.84; P for trend, .007). When the square root of body surface area was included with the other covariates, the relation between female sex and risk of hospital mortality was substantially reduced and was no longer statistically significant. The adjusted OR (women versus men) was 1.18; CI95%, 0.72 to 1.95 (Table 3).

Women were less likely than men to receive internal mammary artery (IMA) grafts (64.8% versus 78.4%, P<.001), and this association persisted after adjustment for clinical, demographic, and treatment variables and body surface area (P<.001). The use of an IMA graft was associated with decreased hospital mortality; the

TABLE 2. Relative Odds of In-Hospital Death Associated With Coronary Artery Bypass Graft Surgery by Body Surface Area

<table>
<thead>
<tr>
<th>Body surface area, m²</th>
<th>All Subjects</th>
<th>Odds Ratio</th>
<th>Adjusted*</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Men</td>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>≥2.0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1.8-1.9</td>
<td>1.75</td>
<td>1.45</td>
<td>1.57</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>1.6-1.7</td>
<td>2.82</td>
<td>1.99</td>
<td>2.27</td>
<td>2.62</td>
<td></td>
</tr>
<tr>
<td>&lt;1.6</td>
<td>4.83</td>
<td>2.84</td>
<td>3.50</td>
<td>4.30</td>
<td></td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;.001</td>
<td>.007</td>
<td>.007</td>
<td>.005</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, comorbidity, unstable angina pectoris, prior coronary artery bypass graft surgery, priority at surgery, ejection fraction, left ventricular end-diastolic pressure, poor cardiac function, percent stenosis of the left main coronary artery, number of diseased coronary arteries, preoperative intravenous nitrroglycerin, and preoperative intra-aortic balloon pump.
Adjusted OR (IMA versus no IMA) was 0.57; CI$_{95\%}$, 0.37 to 0.87). Adjusting for IMA grafting yielded an OR (women versus men) of 1.11; CI$_{95\%}$, 0.67 to 1.84 (Table 3). This logistic regression equation was strongly associated with hospital mortality (model $x^2$ [15 df], 158.8; $P<.001$). To make sure that possible effects of variation on performance among centers was appropriately considered, a random-effects analysis was carried out (data not presented), and the results were almost identical to those of the analysis of the pooled data.

Analysis of Vessel Size

The coronary artery luminal diameter was measured on a series of 945 patients at one institution. The mean luminal diameters of the coronary arteries were larger among men than among women (right coronary artery [n=369 patients]: 2.30 versus 2.20 mm, $P=.123$; mid left anterior descending coronary artery (LAD) [n=714 patients]: 2.03 versus 1.80 mm, $P<.001$; first diagonal branch of the LAD [n=366 patients]: 1.83 versus 1.66 mm, $P<.001$; obtuse marginal branch of the circumflex [n=612 patients]: 2.00 versus 1.86 mm, $P<.001$). The mean relative luminal diameters differed between men and women by 4.3% to 11.3%, corresponding to an 8.5% to 21.4% difference in the luminal areas. There was a strong positive correlation (Pearson's correlation, $r=.83$ to .98) between the probe-determined luminal diameter of the coronary arteries and the median body surface area in each patient group.

The independent contribution of vessel size to risk of hospital mortality was examined among patients having measurements of the mid LAD. The OR for mortality by mid LAD luminal diameter ($<2.5$ versus $\geq2.5$ mm) was 8.59 (CI$_{95\%}$, 1.16 to 63.81, $P=.036$); adjustment for patient risk variables found to be independently associated with mortality (age, sex, prior CABG, comorbidity score, EF, LVEDP, priority at surgery) and body surface area only slightly decreased this OR (OR, 6.10). Thus, those with small mid LAD luminal diameter were at greatly increased odds of hospital mortality even when other patient and clinical risk factors, including body surface area, were considered. With respect to the effect of coronary vessel diameter on the excess mortality experienced by women, the addition of mid LAD luminal diameter to the regression model containing patient risk variables and body surface area resulted in a reduction of 0.17 in the OR for mortality of women versus men.

Causes of Death

Data on primary cause of death for each of the 132 deaths are summarized in Table 4. With the exception of dysrhythmia, women were at greater risk of death in each category; however, respiratory failure, stroke, and "other causes" did not reach statistical significance. Statistically significant differences were found only for heart failure (RD, 2.05; CI$_{95\%}$, 0.89 to 3.22) and hemorrhage (RD, 0.63; CI$_{95\%}$, 0.13 to 1.13), and these differences in rates accounted for 71.1% (54.4% and 16.7%, respectively) of the sex-specific difference in hospital mortality rates.

After adjustment for the patient's sex, age, priority at surgery, and use of an IMA, small body surface area was positively associated with death from heart failure (OR $<1.6$ versus $\geq2.0$ m$^2$, 1.91; $P$ for trend, .039) and hemorrhage (OR $<1.6$ versus $\geq2.0$ m$^2$, 4.17; $P$ for trend, .051) but not with death from other causes. The presence of IMA grafting was independently associated with reduced risk of death from heart failure (OR [IMA versus no IMA], 0.34; CI$_{95\%}$, 0.20 to 0.57; $P<.001$) but was not significantly associated with death from hemorrhage or other causes.

Death in the operating room or within 1 hour after surgery occurred much more frequently among women (OR [women versus men], 3.68; CI$_{95\%}$, 1.63 to 8.14; $P=.0016$); this was true among those having elective surgery (OR, 4.88) and also among those requiring urgent or emergent surgery (OR, 2.84).

Autopsy results were available for 38 of 132 deaths (28.8%). The autopsy rate varied widely by medical center from 2.9% to 67.7% and was highest among men (36.5%) than women (19.0%). Graft closure was found at autopsy in 11.5% of men and in 40.0% of women (Fisher's $P=.076$). One medical center accounted for 55.3% of all autopsies. The autopsy rates at this center were 65.0% of men and 72.7% of women; graft occlusion was found among 15.4% of men and 50.0% of women (Fisher's $P=.146$).

Among individuals who died in the hospital, recent myocardial infarction was reported among 32.8% of women and 23.0% of men (Fisher's $P=.210$).

Discussion

Reports detailing the higher risk of hospital mortality for women after CABG first appeared in the 1970s and represented surgical experience from the late 1960s to the mid 1970s. This regional prospective study found that two decades later, women are still more than twice as likely as men to die while still in the hospital after CABG.

A number of clinical and hemodynamic variables have been found to be associated with a higher risk of hospital mortality for patients undergoing CABG.
These variables include increased age, the necessity for urgent or emergent surgery, the presence of comorbidity, decreased left ventricular EF, increased LVEDP, prior CABG surgery, and increased angiographic severity of coronary artery disease.\textsuperscript{43-46} In the present study, some of the excess risk among women was attributable to older age, to slightly higher comorbidity scores, and to a larger percentage of women having urgent or emergent CABG. However, even after adjustment for these and other listed variables, there remained a 75% higher risk among women.

A strong inverse approximately quadratic relation was evident between hospital mortality rate and body surface area, and this persisted after clinical, demographic, and treatment variables were accounted for. When differences in body surface area were accounted for, female sex was no longer associated with higher hospital mortality. A strong positive correlation between coronary artery luminal diameter and body surface area was also noted. Numerous studies have documented decreased short-term patency in bypass conduits grafted to coronary vessels of small diameter.\textsuperscript{47-53} The sex-specific differences in coronary artery diameter have also been reported recently by Dodge et al.\textsuperscript{54}

Even after clinical, demographic, and treatment variables and urgent or emergent surgery were accounted for, women were less likely than men to receive IMA grafts, and the performance of IMA grafting was significantly associated with decreased mortality. In an analysis of 7105 CABG patients by Cosgrove et al,\textsuperscript{55} IMA was found in multivariate analysis to be associated with decreased risk of surgical morbidity or mortality ($P<.001$). In a multivariate analysis of 2-year mortality rates, Kirklin et al\textsuperscript{56} found that the use of an IMA was associated with lower rates of mortality ($P<.001$). The reasons for the lower frequency of IMA grafting among women are obscure; however, a study by Suma et al\textsuperscript{57} indicated that IMA grafting can be successfully undertaken even among patients of small body size.

Reports attempting to explain the sex difference in mortality associated with CABG include studies by Fisher et al,\textsuperscript{11} Loop et al,\textsuperscript{21} and Khan et al.\textsuperscript{19} The present study and those of Fisher and Loop found that after adjustment for clinical and angiographic variables, patients with smaller body surface area are at a higher risk of hospital mortality after CABG. Despite a body surface area distribution very similar to that found in other studies, Khan et al did not find a significant association between hospital mortality and body surface area; however, this study (which included only 21 deaths among women) had inadequate statistical power. Khan et al did report lower frequency of IMA grafting in women. Khan attributed the difference in mortality to sex-related differences in age and New York Heart Association functional classification.

In the present study, women more often had an acute presentation (urgent or emergent) at the time of CABG, despite having the same extent of coronary artery disease. This finding is consistent with the studies of Fisher et al and Khan et al and is similar to other studies that found an increased severity of angina and symptoms of congestive heart failure in women at the time of CABG, despite similar (or less severe) angiographic disease and similar (or better) left ventricular function.\textsuperscript{9,11,12,18,21,23,25,45} Further understanding of sex-related differences in the relation between hemodynamic status and functional status is needed.

Differences in referral patterns for women and men with suspected coronary artery disease may contribute to the increased frequency of nonselective surgery in women. Other studies have noted different rates of referral for coronary angiography in women compared with men in the presence of noninvasive testing results of coronary artery disease,\textsuperscript{27} the same hospital discharge diagnosis,\textsuperscript{28} and similar clinical history and prior cardiac events.\textsuperscript{29}
Body surface area was positively correlated with coronary artery luminal diameter and was a powerful determinant of the risk of hospital mortality for men and women undergoing CABG. Smaller coronary artery luminal diameter, along with increased risk of death from heart failure among women and the suggestion of an increased risk of recent myocardial infarction and of graft occlusion confirmed by autopsy among women, renews the concern that bypass grafts to smaller coronary vessels are more likely to fail during the perioperative period. However, this etiology is not fully confirmed by these data. A common cause of perioperative heart failure is myocardial ischemia or infarction. Causes of perioperative ischemia include incomplete revascularization, stenosis distal to the anastomosis of a grafted coronary artery, occlusion of a bypass graft, technical problems with graft anastomoses, and inadequate intraoperative myocardial preservation.58 Although studies have shown that smaller coronary artery diameter is a risk factor for graft occlusion, the association between graft occlusion and perioperative myocardial infarction is less clear. One study suggested that the majority of perioperative graft occlusions do not result in myocardial infarction.59 A second study concluded that the majority of perioperative myocardial infarctions are not associated with graft occlusion.60 Further study is needed to better characterize the relation between coronary artery size and perioperative myocardial ischemia and heart failure. In addition, it would be useful to better characterize men and women with respect to the rate of perioperative myocardial infarction, use of aspirin, and anticoagulant use as they relate to postoperative hemorrhage. Quantitative coronary angiography would also be useful to better characterize the extent of coronary artery disease in men and women.

The explanation for the higher risk of hospital mortality among women having CABG is multifactorial. Women’s older age, greater comorbidity, and increased clinical acuity at the time of CABG explained a portion of the observed excess risk. The majority of the excess risk, however, was a consequence of death from heart failure and, to a lesser extent, hemorrhage. Lack of IMA grafting and small body surface area (probably because of its association with coronary luminal diameter) were each associated with increased risk of death from heart failure. Technical factors, graft failure, and inadequate myocardial protection are the likely mechanisms explaining this excess risk.

Appendix

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