Female Gender Is an Independent Predictor of Operative Mortality After Coronary Artery Bypass Graft Surgery
Contemporary Analysis of 31 Midwestern Hospitals

Ron Blankstein, MD; R. Parker Ward, MD; Morton Arnsdorf, MD, MACC; Barbara Jones, MA; You-Bei Lou, PhD; Michael Pine, MD, MBA

**Background**—Women have a higher operative mortality (OM) after coronary artery bypass graft (CABG) surgery than men. Suggested contributing factors have included women’s increased age, advanced disease, comorbidities, and smaller body surface area (BSA). It is unclear whether women’s increased risk factors fully account for this difference or whether female gender within itself is associated with increased OM. We attempted to determine whether, all other factors being equal, there is a significant difference in OM between men and women undergoing CABG.

**Methods and Results**—We retrospectively reviewed a clinical database of 15,440 patients who underwent CABG at 31 Midwestern hospitals in 1999–2000. Each patient record consisted of >400 data elements. Risk-adjusted mortality rates were computed using a predictive equation derived by stepwise logistic regression. Overall, women were older, had a higher incidence of diabetes and valvular disease, and were more likely to be presenting in shock. The OM for the entire population was 2.88% (women 4.24% versus men 2.23%, \( P < 0.0001 \)). Lower BSA was found to be an independent predictor of increased mortality, and a direct inverse relationship between BSA and OM was noted. After adjusting for all comorbidities including BSA, female gender remained an independent predictor of increased mortality (risk-adjusted OM was 3.81% for women and 2.43% for men). Thus, whereas risk adjustment reduced women’s OM from 90% higher than men’s to 22% higher, a significant difference remained.

**Conclusions**—In this contemporary data set from 31 Midwestern hospitals, female gender was an independent predictor of perioperative mortality, even after accounting for all comorbidities, including low BSA. (Circulation. 2005; 112[suppl I]:I-323–I-327.)

**Key Words:** bypass ■ cardiovascular diseases ■ coronary disease ■ surgery

Operative mortality (OM) after coronary artery bypass graft (CABG) operations is considerably higher in women than in men.¹⁻⁰ This disparity between genders has persisted despite of a remarkable decrease in OM for patients undergoing CABG surgery over the last 15 years.¹¹ Whereas some groups have reported a referral bias causing women to present for revascularization at a more advanced stage of disease compared with their male counterpart,⁶ others have attributed the underutilization of internal mammary artery (IMA) grafts as a cause for worse female outcomes. Still others have found no significant difference in CABG OM when men and women of similar risk and body size are compared. Recently, several studies have suggested that women’s lower body surface area (BSA), which is thought to be a surrogate for their smaller coronary vessel size, accounts to a large extent for higher CABG OM.

To date, there have been conflicting reports about whether this difference in outcomes between men and women undergoing CABG surgery persists after accounting for all identifiable risk factors. Previous investigations of gender differences in mortality have predominantly examined data from the early to mid 1990s. They are additionally limited by the fact that the majority of these studies represent data from only a single institution. Thus, we sought to determine whether, all other factors being equal, there is a significant difference in OM between men and women undergoing CABG in a large, multicenter contemporary clinical database.

**Methods**

**Data**

Data were collected for 15,440 consecutive patients who underwent CABG at 31 hospitals in the Midwest between 1999 and 2000. Hospitals ranged from small community hospitals to large academic centers. The clinical database consisted of >400 data elements per patient including variables such as demographics, past medical and procedural histories, vital signs, functional capabilities, laboratory data, coronary angiographic findings, clinical interventions, and complications. Data were submitted to Michael Pine and Associates, Inc. for evaluation of risk-adjusted clinical outcomes and their
relation to processes of care by hospitals applying for inclusion in the
Anthem Coronary Services Network. All of the data were masked to
preserve patient confidentiality. Each institution certified its data as
complete, agreed to release billing data to validate the completeness
of its submission, and authorized use of its data for research
purposes. Data consistency and plausibility were confirmed by
examination of marginal values of potential variables.

Analysis
Stepwise logistic regression was performed using Statistical Analy-
sis Software (version 8.2, SAS Institute Inc.) to derive an equation
that predicts the risk-adjusted mortality rate for a given patient
undergoing CABG. All of the descriptors of preoperative status that
had a significant univariate association with increased mortality were
eligible for inclusion. Continuous variables that had nonlinear
associations to mortality were represented as a set of dichotomous
variables, which corresponded to different ranges of values (i.e., age
< 85, age 75 to 85, age 65 to 75, and age < 65). Standard estimates
were used to calculate odds ratios (ORs) and 95% CIs for each
independent predictor. The initial regression derived purposely
omitted gender and BSA to isolate their effect on OM after all of the
other significant variables have been accounted for.

The goal of the next part of the analysis was to determine whether
BSA could additionally explain the mortality gap between men and
women. BSA was calculated for each patient using the Mosteller
formula (BSA = [height (cm) × weight (kg)]/3600)1/2). After analyz-
ing the distribution of BSA in our study population, we defined a low
BSA as <1.8. This new dichotomous variable was now added to the
initial predictive equation, and the new model was recalibrated. To
additionally explore the relationship between OM and BSA, all
15,440 patients were divided into 5 quintiles of ascending BSA. This
was done by arranging all of the patients in increasing order of BSA.
Patients were then divided into 5 equal groups from lowest BSA
(bottom 20%) to highest BSA (top 20%). The adjusted OM for each
quintile was calculated.

In a subsequent analysis, we attempted to additionally enhance the
OM prediction model by introducing process variables, such as
cross-clamp time and type of bypass vessels used. Finally, we
examined the OM for men and women undergoing CABG with or
without a history of prior open heart surgery and with or without
associated valvular surgery to determine whether the disparity in
outcomes persists for different types of operations.

Results
Patient Population
Of the 15,440 patients who underwent CABG, 10,417 were men
(67.47%), and 5,023 were women (32.53%). The average age of
all of the patients was 64.3 years (66.4 for women and 63.3 for
men). A comparison of risk factors for men and women (Table
1) shows that there were significant differences in the 2 popu-
lations. In general, women were older and had a higher incidence
of diabetes, renal failure, class III or IV New York Heart
Association (NYHA) heart failure classification, valvular disease,
and shock. On the other hand, men were more likely to
have 3-vessel disease and moderate-to-severe systolic dysfunc-
tion. Both men and women had a similar rate of single-vessel,
double-vessel, and triple-vessel disease. There was also an
identical proportion of patients with left main disease and urgent,
emergent, and elective cases.

Mortality Analysis
The unadjusted OM for the entire population was 2.88%.
Women’s OM was approximately twice as high as men’s
(4.24% versus 2.23%, P < 0.0001).

Using the risk-adjusted mortality model shown in Table 2
(without accounting for gender or BSA), the predicted mortali-
ties were 3.39% for women and 2.64% for men. As expected,
these predictions reflect the increased incidence of comorbid
disease in the female population. The observed OM for each
gender was then adjusted by calculating the ratio of observed-
to-predicted OM. This analysis (Figure 1) demonstrated a
significant reduction in the gender gap in OM from 90% to 49%.

Next, we tried to determine whether adjusting for low BSA
may additionally reduce the apparent disparity in OM between
genders. When lower BSA was introduced to the
risk-adjusted mortality model, it proved to be an independent
predictor of increased mortality; in other words, even after
adjusting for all of the identifiable risk factors, patients with
low BSA had worse mortality. Using this new model, the
predicted mortality was now 3.81% for women and 2.43% for
men. Again, the observed OM for each gender was adjusted
by calculating the ratio of observed-to-predicted OM (Figure
2). As a result, the gender mortality gap now additionally
narrowed from 49% to 22%.

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**TABLE 1. Patient Characteristics by Gender**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Female (%)</th>
<th>Male (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 55 years</td>
<td>15.4</td>
<td>22.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Age 55–64 years</td>
<td>23.9</td>
<td>29.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>34.6</td>
<td>30.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Age 75–84 years</td>
<td>24.5</td>
<td>16.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Age &gt; 85 years</td>
<td>1.5</td>
<td>1.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Any valvular disease</td>
<td>13.2</td>
<td>9.3</td>
<td>0.000</td>
</tr>
<tr>
<td>COPD</td>
<td>25.4</td>
<td>25.8</td>
<td>0.579</td>
</tr>
<tr>
<td>CVA</td>
<td>9.1</td>
<td>7.1</td>
<td>0.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40.6</td>
<td>30.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6.2</td>
<td>4.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe aortic calcification</td>
<td>3.7</td>
<td>2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Shock or arrest/CPR</td>
<td>2.3</td>
<td>1.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Left main stenosis &gt;50%</td>
<td>19.1</td>
<td>19.6</td>
<td>0.416</td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>6.1</td>
<td>6.3</td>
<td>0.619</td>
</tr>
<tr>
<td>Double-vessel disease</td>
<td>25.6</td>
<td>25.6</td>
<td>0.975</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>6.1</td>
<td>6.3</td>
<td>0.619</td>
</tr>
<tr>
<td>NYHA class I</td>
<td>0.6</td>
<td>0.5</td>
<td>0.674</td>
</tr>
<tr>
<td>NYHA class II</td>
<td>3.4</td>
<td>2.4</td>
<td>0.000</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>6.0</td>
<td>4.6</td>
<td>0.000</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>6.4</td>
<td>3.8</td>
<td>0.000</td>
</tr>
<tr>
<td>EF - normal</td>
<td>64.3</td>
<td>58.5</td>
<td>0.000</td>
</tr>
<tr>
<td>EF - mild</td>
<td>16.2</td>
<td>19.5</td>
<td>0.000</td>
</tr>
<tr>
<td>EF - moderate to severe</td>
<td>16.3</td>
<td>18.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Elective procedure</td>
<td>71.1</td>
<td>72.7</td>
<td>0.055</td>
</tr>
<tr>
<td>Urgent or emergent</td>
<td>8.3</td>
<td>7.5</td>
<td>0.094</td>
</tr>
<tr>
<td>ASA class 5 (unlikely to survive 24 hr)</td>
<td>1.3</td>
<td>1.0</td>
<td>0.248</td>
</tr>
<tr>
<td>Use of IMA graft</td>
<td>76.8</td>
<td>82.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Prior open heart surgery</td>
<td>5.5</td>
<td>8.2</td>
<td>0.000</td>
</tr>
<tr>
<td>Reoperation</td>
<td>5.4</td>
<td>5.9</td>
<td>0.259</td>
</tr>
</tbody>
</table>

ASA, American Society of Anesthesiologists Classification; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; CPR, cardiopulmonary resuscitation; EF, ejection fraction; IMA, internal mammary artery.
Use of Process Variables to Improve OM Prediction Model

IMA Comparisons
IMA grafts were used in 76.8% of women and 82.3% of men (P=0.0001). Because the use of an IMA graft is associated with reduced OM, some studies suggest that its underutilization in women would expose them to an increased surgical risk. Hence, we attempted to determine whether the reduced use of IMA grafts in women accounts for any of the observed mortality differences between men and women. We found that after adjusting for other patient characteristics, including low BSA, the use of IMA grafting did not have a significant effect on OM.

Perfusion Clamp Time Analysis
Of all of the surgical process variables examined, the only independent predictor of OM was perfusion clamp time. This variable was introduced into the OM prediction model (with low BSA included), and the regression equation was recalibrated (OR=3.41, 95% CI 2.65 to 4.42 for perfusion time >140 minutes; OR=1.58, 95% CI 1.14 to 2.21 for perfusion time 120 to 140 minutes). However, when the predicted mortality rates for each gender were calculated using this model (see Figure 3), there was no additional reduction in the gender gap in OM as compared with the prior model (Figure 2). Thus, longer perfusion clamp times did not add any significant value in explaining the gender difference in OM.

TABLE 2. Independent Predictors of OM After CABG Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65–74 years</td>
<td>2.84 (2.16–3.77)</td>
</tr>
<tr>
<td>Age 75–84 years</td>
<td>4.73 (3.56–6.33)</td>
</tr>
<tr>
<td>Age ≥85 years</td>
<td>8.70 (4.83–15.01)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.73 (1.39–2.16)</td>
</tr>
<tr>
<td>COPD</td>
<td>1.36 (1.09–1.69)</td>
</tr>
<tr>
<td>History of CVA</td>
<td>1.44 (1.06–1.93)</td>
</tr>
<tr>
<td>Renal failure (Cr &gt;2)</td>
<td>1.59 (0.98–2.49)</td>
</tr>
<tr>
<td>Creatinine &gt;2 (no dialysis)</td>
<td>2.57 (1.73–3.74)</td>
</tr>
<tr>
<td>Dialysis (1)</td>
<td>5.88 (3.35–9.84)</td>
</tr>
<tr>
<td>MI within last 7 days</td>
<td>1.73 (1.38–2.17)</td>
</tr>
<tr>
<td>Prior open heart surgery</td>
<td>2.43 (1.80–3.23)</td>
</tr>
<tr>
<td>Associated valvular surgery</td>
<td>2.54 (1.94–3.32)</td>
</tr>
<tr>
<td>Associated nonvalvular open heart surgery</td>
<td>2.04 (1.30–3.09)</td>
</tr>
<tr>
<td>Associated aortic aneurysm or other aortic bypass</td>
<td>1.95 (1.01–3.58)</td>
</tr>
<tr>
<td>Severe aortic calcifications</td>
<td>1.57 (1.06–2.26)</td>
</tr>
<tr>
<td>Left main disease ≥70%</td>
<td>1.35 (1.01–1.78)</td>
</tr>
<tr>
<td>Emergent/urgent</td>
<td>2.42 (1.76–3.29)</td>
</tr>
<tr>
<td>ASA class 5</td>
<td>2.68 (1.66–4.25)</td>
</tr>
<tr>
<td>Preoperative arrest or shock</td>
<td>3.54 (2.33–5.35)</td>
</tr>
<tr>
<td>Systolic BP &lt;90</td>
<td>2.29 (1.01–4.69)</td>
</tr>
<tr>
<td>Preoperative heart rate &gt;110</td>
<td>2.11 (1.31–3.32)</td>
</tr>
</tbody>
</table>

OR for all predictors, P<0.01.

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; Cr, creatinine; MI, myocardial infarction, ASA, American Society of Anesthesiologists Classification; BP, blood pressure.

*After introducing female gender to above core model.
†After introducing both female gender and low BSA to above core model.

CABG Mortality Rates
(adjusting for 21 core variables & BSA)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Observed Mortality</th>
<th>Predicted Mortality</th>
<th>Observed/Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>2.88%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>2.23%</td>
<td>2.43%</td>
<td>0.91</td>
</tr>
<tr>
<td>Females</td>
<td>4.24%</td>
<td>3.81%</td>
<td>1.11</td>
</tr>
</tbody>
</table>

Figure 1. Risk adjustment reduces the CABG mortality gap. Female observed mortality is 90% higher than males (4.24:2.24). The predicted mortality for each gender is calculated by using the equation shown in Table 2. This measure reflects the degree of risk associated with each gender. By calculating the observed/predicted mortality, the mortality rate for each gender is adjusted for their level of risk. A comparison of the 2 genders now shows that female-adjusted mortality is 49% higher than males (1.25:0.84). Hence, this adjustment results in a reduction in the gender gap in operative mortality from 90% to 49%.

Figure 2. Addition of BSA additionally reduces the CABG mortality gap. Female observed mortality is 90% higher than males (4.24:2.24). The predicted mortality for each gender is calculated by using a predictive equation, which now includes all of the variables that are shown in Table 2, as well as low BSA. This measure more accurately reflects the degree of risk associated with each gender. By calculating the observed/predicted mortality, the mortality rate for each gender is adjusted for their level of risk. A comparison of the 2 genders now shows that female-adjusted mortality is 22% higher than males (1.11:0.91). Hence, this adjustment results in a reduction in the gender gap in operative mortality from 90% to 22%.
**Analysis of BSA**

The distribution of BSA for all of the men and women is illustrated in Figure 4. Whereas both genders have a symmetric bell-shaped distribution, as expected, women have lower BSA versus men. Figure 5 shows the adjusted mortality rate for each quintile of BSA. There is a direct inverse relationship between BSA and OM, and, regardless of gender, the lower the BSA, the higher the OM. Additionally, within each quintile, women had higher OM when compared with men of similar size.

**Effect of Type of Surgery**

Table 3 summarizes the unadjusted OM for each gender among 3 different types of surgeries arranged from lowest to highest risk. As is consistent with our previous analysis, women undergoing first-time open heart surgery with or without associated valvular surgery have an OM that is approximately twice as high as men’s. However, when examining the riskiest procedure type (patients who had a prior open heart surgery and now have a valvular surgery in addition to CABG), we notice that women’s OM is nearly 3 times as high compare with that of men. In summary, regardless of the type of surgery, women’s OM is significantly higher than men’s OM, and this difference may become even greater with higher-risk operations.

**Discussion**

This study finds that even after adjusting for all identifiable risk factors, women undergoing CABG continue to have a higher OM than men. Whereas women may appear to have a mortality rate that is 90% higher than their male counterparts, after risk adjustment, this gender gap in OM decreases to 22%. Nevertheless, this gender gap represents an important

**TABLE 3. Unadjusted Mortality for Each Gender By Type of Surgery**

<table>
<thead>
<tr>
<th>Gender</th>
<th>All Patients</th>
<th>No Prior/No Valve</th>
<th>No Prior/With Valve</th>
<th>Prior and Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>2.23%</td>
<td>1.73%</td>
<td>6.41%</td>
<td>6.85%</td>
</tr>
<tr>
<td>Females</td>
<td>4.24%</td>
<td>3.37%</td>
<td>12.24%</td>
<td>20.00%</td>
</tr>
</tbody>
</table>

(No) Prior means (no) prior open heart surgery; (No) valve means (no) associated valvular surgery at the time of CABG. All mortality rates are unadjusted.
disparity in operative outcomes which, if reduced, could translate into many saved lives.

Previous studies examining gender differences in OM after CABG have found similar results. However, many of these studies were limited because they used older data and often only represented single institutions. Given our contemporary data set, which represented both academic and community hospitals, we were particularly interested to determine whether the many recent impressive improvements in operative outcomes have also translated into improvement in women’s outcomes relative to men.

The methodology used in this study was unique because it enabled us to describe what proportion of women’s higher risk can be attributed to their higher incidence of comorbidities, such as advanced age, diabetes, and heart failure, versus what proportion is attributable to their smaller body size. This method of risk attribution found that whereas much of women’s excess mortality is attributable to identifiable gender differences at baseline, the cause of the remainder of the difference is unknown.

The pathophysiologic reasons for the influence of BSA on mortality are not completely clear. Some investigators have found a correlation between patient body size (BSA) and patient coronary vessel size. Smaller vessel size may imply more operative technical difficulties. Small vessels have also been demonstrated to be independent risk factors for coronary dissection, abrupt closure, and other complications.

Future Research

Given these findings, a strong emphasis should be placed on identifying methods to reduce women’s CABG OM. To accomplish this, additional research should attempt to identify additional factors that contribute to the gender gap in CABG OM. Potential factors may include surgical process variables. For instance, recent studies have suggested no difference in outcomes between men and women when off-pump CABG procedures were used. Other important factors that may help to explain the poor outcomes in women include the effects of body fat composition, which renders tissues and blood vessels less likely to heal and more likely to dissect. Finally, much remains unknown about the role of hormones and specifically the postmenopause state that may impart a higher risk for women. At the present time, our findings highlight the need for additional research to more precisely identify the cause for women’s worst outcomes after cardiac surgery.

Limitations

The limitations of our study arise primarily from its observational design. For example, the decision to use a specific technology or specific medications was not controlled. Furthermore, data were collected by many different individuals in different sites and, hence, are subject to some lack of uniformity. For the purposes of our analysis, variations in data quality should not influence our results, because it seems unlikely that variations in data collection or event reporting among sites would vary by gender.

In spite of these limitations, by using a large database, we were able to adjust for many important risk factors. Furthermore, our data represented hospitals of various sizes and settings, making the data more representative of current practice patterns than single-site databases.

What Is the Optimal Revascularization Strategy for Women?

Because women also have worse outcomes when undergoing percutaneous interventions, gender alone should not be a significant factor when deciding the method of coronary revascularization. The result of this study should not be used to deter bypass surgery operations in women but rather, at least for now, to draw close attention to all modifiable perioperative risk factors.

Conclusions

In this contemporary data set from 31 Midwest hospitals, women undergoing coronary artery bypass had more comorbidities and were overall sicker than men. Subsequently, the majority of women’s increased CABG mortality versus men was explained by their increased incidence of comorbidities. However, even after adjusting for all of the identifiable risk factors, including low BSA, female gender remained an independent predictor of peri-operative mortality. Irrespective of gender, low body surface area is an independent predictor of OM.

References

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