

# Cardiac and Neurologic Complications Identify Risks for Mortality for Both Men and Women Undergoing Coronary Artery Bypass Graft Surgery

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**Background:** Despite a number of studies showing that women and men respond to coronary artery bypass graft surgery differently, it is not known whether variables associated with mortality are the same for women and men. The purpose of this study was to identify variables independently associated with mortality for women undergoing coronary artery bypass graft surgery.

**Methods:** Single-institutional data were prospectively collected from 5,113 patients (1,558 or 30.5% women) undergoing coronary artery bypass graft surgery. The database was reviewed for patient characteristics and operative outcomes based on sex. Complications evaluated included low cardiac output syndrome (cardiac index  $< 2.0 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  for  $> 8 \text{ h}$ , regardless of treatment), stroke (new permanent global or focal motor deficits), Q-wave myocardial infarction, postoperative atrial fibrillation, and operative mortality.

**Results:** Women were older than men, and they were more likely to have preexisting hypertension, diabetes, and a history of stroke. Operative mortality for women was higher than for men (3.5% vs. 2.5%,  $P < 0.05$ ). Compared with men, women were more likely to experience a postoperative myocardial infarction, stroke, and low cardiac output syndrome. When performing analysis on data from both sexes separately, low cardiac output syndrome, new stroke, myocardial infarction, and duration of cardiopulmonary bypass were independently associated with mortality for women and men both. Patient age was not independently associated with risk for mortality for women, but it was for men. However, when the authors combined both sexes in the logistic regression analysis, the age-sex interaction was not significant ( $P = 0.266$ ), indicating that there was insufficient evidence to assert that age has a different effect on mortality for men and women.

**Conclusions:** These data confirm that women have higher perioperative mortality after coronary artery bypass graft surgery compared with men. A higher frequency of cardiac and neurologic complications seem to account to a large extent for the higher operative mortality for women. Factors indepen-

dently associated with perioperative mortality are generally similar for women and men.

CORONARY artery disease is the most frequent cause of death for women in the United States.<sup>#</sup> Increasingly, coronary artery bypass graft (CABG) surgery is used for women as an effective treatment for this disease. Women now account for nearly 30% of patients undergoing CABG surgery (compared with 11-15% three decades ago) and 40% of the patients older than 80 yr of age.<sup>1-16</sup> These trends are noteworthy insofar as women are reported to have higher morbidity and mortality after CABG surgery than men.<sup>1-15</sup> Compared with men, the onset of symptomatic coronary artery disease in women is delayed 10-15 yr until after menopause.<sup>17</sup> Therefore, women are referred for CABG surgery at an older age than men and with more comorbid conditions, such as diabetes and hypertension.<sup>1-15</sup> These factors, along with bias in the referral of women for myocardial revascularization and technical difficulties with surgery due to smaller coronary artery size, are the predominant explanations for the poorer outcomes from CABG surgery for women.<sup>1-15,18,19</sup> However, for the most part, previous investigations that have sought to identify reasons for adverse operative outcomes for women have not adequately considered whether postoperative neurologic complications contribute to operative mortality.

Because of the increasing prevalence of coronary artery disease in women (nearly 1 million new cases diagnosed each year) along with the general aging of the US population, the number of elderly women who require CABG surgery will likely continue to increase.<sup>7,16,17</sup> Understanding factors that predispose women to perioperative mortality is essential to foster strategies to improve patient outcomes. Despite a number of studies showing that women and men respond to CABG surgery differently, it is not known whether variables associated with perioperative mortality are the same for women and men. The purpose of this study was to identify variables independently associated with mortality for women undergoing CABG surgery.

## Methods

Using methods approved by the Human Studies Committee of Washington University (St. Louis, MO), clinical data were prospectively collected from 5,113 adult patients undergoing CABG surgery at Barnes-Jewish Hospi-

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Received from the Department of Anesthesiology; the Division of Cardiothoracic Surgery, Department of Surgery; the Cardiovascular Division, Department of Medicine; and the Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri. Submitted for publication October 7, 2000. Accepted for publication April 25, 2001. Supported by institutional funds from the Department of Anesthesiology, Washington University School of Medicine. Presented in part at the annual meeting of the American Society of Anesthesiologists, Dallas, Texas, October 11, 1999.

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# American Heart Association: Women and Cardiovascular Disease Biostatistical Fact Sheet. Available at: <http://www.americanheart.org/biostats/biowo.htm>. Accessed 2000.

tal (St. Louis, MO) from January 1990 to August 1996. The data were collected daily by trained and experienced research nurses using standardized forms as previously described.<sup>20</sup> Data were entered into an institutional computerized database by dedicated research staff. Medical and demographic characteristics collected are similar to those previously described and included information regarding previous stroke or reversible neurologic events.<sup>20</sup> Patients received routine institutional perioperative care that included an opioid-based anesthetic supplemented with volatile anesthetics and skeletal muscle relaxants. Cardiopulmonary bypass was performed with membrane oxygenators and arterial line filters using mild hypothermia (28–33°C). After surgery, patients were monitored with continuous telemetry electrocardiography until hospital discharge to document the occurrence of atrial fibrillation.

Postoperative complications were documented, including myocardial infarction (new Q waves on the 12-lead electrocardiogram), low cardiac output syndrome (cardiac index  $< 2.0 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  for  $> 8$  h after surgery, regardless of treatment), atrial fibrillation, stroke, and death within 30 days after surgery or during the same hospitalization as surgery. All patients had 12-lead electrocardiography performed before surgery and on the morning of the first 3 postoperative days. All electrocardiographs were interpreted by a cardiologist, and the diagnosis of myocardial infarction was based on this review. Stroke was defined as any new permanent global or focal neurologic deficit that could not be attributed to other neurologic (e.g., dementia) or metabolic abnormalities, hypoxia, or drugs, and it excluded reversible cerebral ischemic events. Postoperative physical examinations were performed daily in all patients by the attending medical staff. All clinically suspected strokes were confirmed by a neurologist and often by computed tomography or magnetic resonance imaging of the head. Operative death was defined as death during the same hospitalization as surgery or death within 30 days after surgery. This endpoint was ascertained daily by the data coordinators reviewing medical records on the hospital ward and daily review of hospital-wide patient information. Patients discharged before this time were contacted on the closest business day to the 30th postoperative day. If the patient or his or her family could not be contacted, information about the health status of the patient was obtained from the patient's primary care physician or cardiologist. Data regarding the presence or absence of operative mortality were available for all patients.

#### Statistical Analysis

Data analysis was performed using version 6.12 of SAS (SAS Institute, Cary, NC). Patient characteristics and outcomes were compared between men and women and separately within the sexes dichotomized based on op-

**Table 1. Patient Characteristics, Including Complications after CABG Surgery Based on Gender**

	Women (n = 1,558)	Men (n = 3,555)	P Value
Age (mean $\pm$ SD)	67 $\pm$ 10	65 $\pm$ 10	$< 0.0001$
Hypertension (%)	76.9	62.8	$< 0.001$
Diabetes (%)	39.7	26.4	$< 0.0001$
Previous stroke (%)	9.6	7.3	$< 0.01$
Cardiopulmonary bypass time (min)	120 $\pm$ 49	125 $\pm$ 44	$< 0.001$
Cross-clamp time (min)	61 $\pm$ 23	65 $\pm$ 44	$< 0.0001$
Postoperative MI (%)	3.4	1.9	$< 0.01$
Low cardiac output syndrome (%)	5.9	3.6	$< 0.0014$
Postoperative atrial fibrillation (%)	34.5	33.7	0.58
Postoperative stroke (%)	3.2	2.5	$< 0.0001$
Mortality rate (%)	3.5	2.5	$< 0.05$

CABG = coronary artery bypass graft; MI = myocardial infarction.

erative mortality. Univariate comparisons were performed with chi-square tests for dichotomous variables and with analysis of variance for ordered categorical and continuous variables. Nonparametric analysis was used for the latter when regression residuals suggested that the model fit was poor. Stepwise logistic regression was used to identify independent predictors of mortality for both sexes. Variables entered into the initial logistic models included those variables that had a univariate *P* value of less than 0.2. The final model included age and all variables with an independent significance level of  $P < 0.1$ . In the logistic model, age and cardiopulmonary bypass duration were divided by 10 so that the odds ratio reflected changes in decades and 10 min, respectively. A sex-age interaction was included in a logistic regression model that included all subjects to test for significant differences between sexes in the association between increasing age and mortality. The quality of the fit of the logistic model was tested using the Hosmer and Lemeshow goodness-of-fit test. Data for continuous variables are presented as mean  $\pm$  SD.

## Results

Patient characteristics for women and men are listed in table 1. Women were older than men, and they were more likely to have hypertension, diabetes, and a history of a stroke. The duration of cardiopulmonary bypass and aortic cross-clamping was shorter for women compared with men. Postoperative myocardial infarction, low cardiac output syndrome, and new stroke were more common in women, but the rates of other complications did not differ between sexes. The mortality rate for women was significantly higher than for men (3.5% *vs.* 2.5%,  $P < 0.05$ ).

Univariate predictors of mortality analyzed separately for women and men are listed in table 2. The duration of

**Table 2. Univariate Predictors of Mortality after CABG Surgery Considered Separately by Gender**

	Women			Men		
	Mortality (n = 57)	No Mortality (n = 1,501)	P Value	Mortality (n = 93)	No Mortality (n = 3,462)	P Value
Age (mean ± SD)	69 ± 9	67 ± 10	0.13	68 ± 10	65 ± 10	< 0.001
Hypertension (%)	77.2	76.9	0.96	73.1	62.6	< 0.05
Diabetes (%)	43.9	39.5	0.51	32.3	26.3	0.20
Previous stroke (%)	10.5	9.6	0.817	15.1	7.1	< 0.01
CPB time (min)	156 ± 58	119 ± 48	< 0.0001	165 ± 59	124 ± 43	< 0.0001
Cross-clamp time (min)	68 ± 26	61 ± 23	< 0.05	78 ± 33	65 ± 25	< 0.0001
Low cardiac output (%)	37.5	4.7	< 0.0001	34.8	2.7	< 0.0001
Postoperative MI (%)	16.0	2.9	< 0.0001	12.8	1.6	< 0.0001
Postoperative atrial fibrillation (%)	40.4	34.3	0.34	43.0	33.4	0.06
Postoperative stroke (%)	15.8	2.8	< 0.0001	10.8	1.2	< 0.0001

CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; low cardiac output syndrome =  $CI < 2.0 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  for  $\geq 8$  h, regardless of treatment; MI = myocardial infarction based on electrocardiographic criteria.

cardiopulmonary bypass and aortic cross-clamping were longer for both women and men with operative mortality compared with patients of the same sex who survived. Postoperative myocardial infarction, low cardiac output syndrome, and postoperative stroke were significant univariate predictors of operative mortality for men and women both. Other univariate predictors of mortality differed between sexes. Whereas age, hypertension, previous stroke, and new onset of atrial fibrillation after surgery were associated with mortality for men, these variables were not different among women with and without operative mortality.

The results of the multivariate logistic regression analysis are listed in table 3. After adjusting for age and other variables that differed between survivors and nonsurvivors, low cardiac output syndrome, postoperative stroke, perioperative myocardial infarction, and duration of cardiopulmonary bypass were independently associated with mortality for men and women both. In contrast to men, there was no significant independent association between age and perioperative mortality for women when the sexes were considered separately in the analysis.

To better understand the association between sex, age, and mortality, logistic regression models that included both sexes were used. When we evaluated the age-sex interaction, sex was not a significant predictor of mor-

tality ( $P = 0.266$ ). These results indicate that despite the nonsignificance of age as a predictor for mortality for women when analyzed separately, we do not have sufficient evidence to claim that older age is a more important predictor of operative mortality for men than women. Although mortality was significantly greater for women compared with men, this significance was lost when sex was included as a predictor in these models in combination with either low cardiac output syndrome ( $P = 0.284$ ), postoperative stroke ( $P = 0.152$ ), or postoperative myocardial infarction ( $P = 0.233$ ). Therefore, the unadjusted significant differences in perioperative mortality for women and men could be explained by any one of these three complications, all of which occurred significantly more often in women compared with men (table 1).

## Discussion

The results of this study confirm that, compared with men, women undergoing CABG surgery are older, have more preexisting medical conditions, and have higher perioperative mortality. We found that women have a higher frequency of stroke and cardiac complications than men. Based on multivariate logistic regression analysis of operative outcomes for each sex considered separately, we found that low cardiac output syndrome, stroke, perioperative myocardial infarction, and duration

**Table 3. Independent Predictors of Mortality after CABG Surgery Separately Considered by Gender**

	Women			Men		
	Odds Ratio	95% CI	P Value	Odds Ratio	95% CI	P Value
Low cardiac output	9.25	4.73–18.10	< 0.0001	8.13	4.59–14.40	< 0.0001
Postoperative stroke	5.00	1.95–12.80	0.0008	6.35	2.67–15.10	< 0.001
Postoperative MI	3.41	1.37–8.49	0.008	5.61	2.57–12.20	< 0.0001
CPB duration*	1.05	1.01–1.08	0.009	1.15	1.10–1.20	< 0.0001
Age†	1.19	0.81–1.83	0.293	1.55	1.18–2.03	< 0.001

\* Odds ratio represents risk for mortality in increments of 10 min of duration of cardiopulmonary bypass. † Odds ratio represents risk of mortality in increments of 10 yr of age.

CPB = cardiopulmonary bypass; low cardiac output syndrome = cardiac infarction  $< 2.0 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  for  $\geq 8$  h, regardless of treatment; MI = myocardial infarction; CABG = coronary artery bypass graft.

of cardiopulmonary bypass were independently associated with risk for mortality for women. These same risk factors, in addition to age, identified risk for perioperative mortality for men.

Technical difficulty with surgery due to smaller coronary artery size has been widely suggested to contribute substantially to poorer outcomes for women undergoing CABG surgery.<sup>1,2,4,11,12</sup> However, some reports have found that body size (a surrogate of coronary artery size) is not a predictor of operative mortality for women.<sup>5,8,10,13,15</sup> Others have shown that women are no more likely than men to have small coronary arteries (diameter  $\leq 1.5$  mm) despite having smaller body size and that they are not at higher risk for coronary artery bypass graft occlusion than men.<sup>13,14</sup> It has been suggested that the discrepancy between these earlier results and the latter studies might be due to improvements in surgical technique and the wider use of antiplatelet drugs.<sup>8,10,13,14</sup> Regardless of mechanism, our data show that two cardiac complications, low cardiac output syndrome and perioperative myocardial infarction, are important causes of operative mortality for women and men both. Whether small coronary artery size, incomplete revascularization, or other factors (*e.g.*, preexisting impaired ventricular function, poor myocardial protection during aortic cross-clamping, incomplete revascularization, and postoperative bypass graft occlusion) contributed to the causation of these outcomes cannot be ascertained by this study.<sup>12</sup>

Postoperative stroke is recognized as an important source of prolonged hospital stay, higher hospital cost, and increased mortality after cardiac surgery.<sup>6,20-22</sup> Previous investigations of perioperative mortality for women after CABG surgery have not clearly evaluated the importance of stroke, especially in relation to other risk factors, particularly cardiac complications. Therefore, our finding that stroke is second only to low cardiac output syndrome as a risk factor for mortality for women provides an explanation for operative mortality unrelated to traditional explanations, such as smaller coronary arteries.<sup>1,2,4,11,12</sup> The majority of perioperative strokes result from cerebral embolism, although cerebral hypoperfusion during cardiopulmonary bypass, periods of perioperative hypotension, or both may also contribute to cerebral injury.<sup>20-22</sup> Atherosclerosis of the ascending aorta is an important source of cerebral embolism and one of the most important risk factors for strokes after cardiac surgery.<sup>20,22-25</sup> One possible explanation for the higher frequency of stroke for women compared with men may be that women undergoing cardiac surgery have a higher prevalence of atherosclerosis of the ascending aorta than men. In a recent study involving nearly 3,000 patients, we found that after adjusting for risk factors, including age, diabetes, hypertension, presence and severity of atherosclerosis of the ascending aorta (documented with epiaortic ultrasound), and se-

verity of carotid artery stenosis, female sex was independently associated with increased risk for stroke.<sup>20</sup> A more recent study of a large multicenter database confirmed that female sex is independently associated with increased risk for stroke after cardiac surgery.<sup>26</sup> Therefore, the higher susceptibility for perioperative stroke for women compared with men cannot be explained by known risk factors, including atherosclerosis of the ascending aorta and carotid arteries.

Age has been widely reported to add incremental risk for mortality from cardiac surgery and to be an important factor in explaining adverse operative outcomes for women compared with men.<sup>3,4,6-9,11,13,16,21</sup> However, Gardner *et al.*<sup>5</sup> noted that although mortality after CABG surgery was significantly related to older age, when adjusted for sex, age-related mortality was significant only for men. More recent analyses have shown that women are at higher risk for mortality after CABG surgery irrespective of age, with the exception of reoperations for patients older than 70 yr of age.<sup>15</sup> In this investigation, when considering the sexes separately and after adjusting for postoperative complications, we found that age was independently associated with mortality only for men, not for women. This suggestion that age may be a more important predictor of mortality for men was further evaluated using a logistic model that included both sexes and that focused on the age-sex interaction. The absence of significance for this interaction ( $P = 0.266$ ) indicates that although our data provided some suggestion that age may have been a more important predictor of perioperative mortality for men than for women, the evidence is inconclusive.

In this study, we sought to focus on cardiac and neurologic complications of CABG surgery because of their overwhelming importance for patient outcomes. We did not perform exhaustive analysis of the relation between other preoperative risk factors and mortality for women. However, we did consider the major comorbid conditions reported to differ between men and women undergoing CABG surgery.<sup>1-15</sup> Although women and men are referred for CABG surgery with different risk profiles, for any given risk factor, women are more likely than men to have operative mortality.<sup>15</sup> Therefore, it seems unlikely that more extensive profiling of patient preoperative risk would drastically alter our results. Our intention was not to develop risk predictive models as a means of identifying before surgery the likelihood of operative mortality. These data from large multicenter studies have previously been reported.<sup>15</sup> Regardless, our data confirm that women have higher perioperative mortality after CABG surgery compared with men. A higher frequency of cardiac and neurologic complications seem to account to a large extent for the higher operative mortality for women. Risk factors independently associated with perioperative mortality are generally similar for women and men.

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