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Association of gender with morbidity and mortality after isolated coronary artery bypass grafting. A propensity score matched analysis ☆,☆☆,★

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ABSTRACT

Introduction: There is conflicting evidence about the impact of gender on outcomes after coronary artery bypass grafting (CABG).
Methods: We performed a multivariate logistic regression and propensity score matched analyses in 13,115 patients (75% men) who underwent CABG between January 1, 1995 and December 31, 2009. The primary outcome was in-hospital mortality. Secondary outcomes included post-operative respiratory failure, stroke, myocardial infarction, sternal and leg wound infections, atrial fibrillation (AF), renal failure, need for postoperative intra-aortic balloon pump (IABP) support, and length of hospital stay.
Results: A higher proportion of women (184; 5.6%) suffered in-hospital death compared to men (264; 2.7%), $p<0.0001$. After propensity score matching ($n=3600$ total, 1800 in each group), female gender was an independent predictor of mortality after isolated CABG (odds ratio [OR] = 1.84; 95% confidence interval [CI] 1.22–2.78). Women also experienced a higher incidence of postoperative complications including stroke (3.8% vs. 2.3%, OR 1.37; 95% CI 1.08–1.73) and leg wound infection (3.4% vs. 1.7%, OR 1.75; 95% CI 1.36–2.54) on multivariate regression analyses. However, these differences were not significant after propensity score matching. We also observed a lower risk of post-operative AF (21.2% vs. 22.1%, OR 0.78; 95% CI 0.70–0.86) in women that remained significant after propensity matching (O.R. 0.76; 95% C.I. 0.65–0.90). Length of hospital stay was longer in women compared with men (11.9 ± 9.0 vs. 10.4 ± 9.2 days, $p<0.0001$).

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Conclusions: Female gender is an independent predictor of increased mortality and a lower incidence of post-operative AF after isolated CABG.

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1. Introduction

Post-operative outcomes in women undergoing coronary artery bypass grafting (CABG) have been an issue of intense investigation due to higher post-operative mortality and morbidity observed in this group of patients [1–7]. Although women comprise less than 30% of all the patients undergoing CABG, they experience a higher post-operative risk of mortality [1,2]. Several gender specific factors have been put forth to explain these incongruent outcomes in women after CABG. Women in general live longer than men and therefore present with symptomatic coronary artery disease (CAD) at a much later age [1,3–5]. Female gender has been reported as an independent predictor of poor post-operative outcomes including mortality after CABG [1,2,6,7]. Several pre-operative risk scoring systems including EuroSCORE and STS score (Society for Thoracic Surgeons Risk Modeling) include female gender as one of the predictors for worse post-CABG outcomes [8,9]. Men and women also differ in the degree of various pre-morbid conditions including hypertension, diabetes mellitus, dyslipidemia, peripheral arterial disease(PAD), congestive heart failure(CHF) and stable or unstable angina pectoris [3,6,7,10]. Apart from increased mortality, several post-operative complications including myocardial infarction(MI), prolonged mechanical ventilation, hemodynamic support, deep sternal wound infections, post-operative sepsis and respiratory failure have also been reported to be higher in women after CABG [1,2,7,11–15].

Review of existing literature on gender specific post-operative outcomes in patients undergoing CABG shows largely cases series and registries. With the exception of a few [7,16,17], most of these studies reported unadjusted outcomes and did not report adjusted outcomes (i.e., multivariate regression or propensity matching) to reduce variability (referral bias, selection bias) in the available data. We therefore planned to conduct a propensity score matched analysis of all the patients who underwent CABG at Texas Heart Institute, Houston, Texas USA using prospectively collected data to address the issue of disparity in post-CABG outcomes in relation to gender.

2. Methods

This study was a retrospective analysis of all consecutive patients who underwent CABG at the St. Luke's Episcopal Hospital/Texas Heart Institute from January 1, 1995, through December 31, 2009. The institutional review board at St. Luke's Episcopal Hospital approved the study protocol. Patients undergoing additional concomitant procedures including surgical valve replacement, aortic root replacement, or left ventricular assist device implantation were excluded. The study population (n = 13,115) was subsequently divided into 2 groups based on gender: men (n = 9848, 75.1%), and women (n = 3267, 24.9%). Patient pre-operative clinical and socio-demographic variables, medication use, details of the procedure, and post-operative variables were obtained from the prospectively collected Texas Heart Institute Research Database (THIRDBase).

The primary outcome was in-hospital mortality, defined as death during the index hospitalization for CABG surgery. Secondary outcomes of interest included: post-operative respiratory failure (failure to extubate in the first 24 h after CABG surgery), post-operative renal insufficiency, post-operative ischemic stroke, post-operative myocardial infarction (MI), infections, post-operative atrial fibrillation (AF), post-operative ventricular tachycardia (VT), and length of hospital stay. Postoperative renal insufficiency was defined as the occurrence of acute tubular necrosis, acute interstitial nephritis, postoperative anuria, or any increase in serum creatinine deemed clinically significant by the treating physician. Post-operative MI was defined as the appearance of new Q waves on electrocardiogram, increased levels of creatine kinase-MB isoenzyme (> 5% of upper limit of normal), a new regional wall motion abnormality (other than paradoxical septal motion) on echocardiogram, or the presence of MI at autopsy. Ischemic stroke was defined as clinical evidence of a focal neurologic deficit along with a radiologic defect on computed tomogram or magnetic resonance imaging scan of the brain. Post-operative AF was defined as the occurrence of atrial fibrillation of any duration during the hospitalization for the index surgery deemed to be clinically significant by the treating physician. Post-operative VT was defined as occurrence of sustained (≥ 30 s or requiring intervention for termination) or non-sustained (≤ 6 beats or < 30 s) during hospitalization for index surgery. All patients were on continuous telemetry throughout their hospital stay, and any episodes of AF, or VT were included in the analysis. For the purpose of analyses, a low left ventricular ejection fraction (LVEF) was defined as LVEF < 50% on pre-operative trans-thoracic two dimensional echocardiogram.

All statistical analyses were performed using SAS statistical software (SAS Institute, Cary, North Carolina). The two patient groups were compared in terms of the presence of pre-operative risk factors. Differences between the two groups were evaluated by chi-square test for discrete variables and independent samples Student's *t* test for continuous variables. A stepwise multivariate logistic regression model was subsequently used to control for potential confounders and to ascertain which variables were independently associated with primary or secondary outcomes. Subsequently, all pre-operative variables described in Table 1 were used in the multivariate logistic regression model. In order to minimize selection bias, we then performed propensity score analyses. Propensity scores were estimated for each patient using unconditional logistic regression. Men and women were matched 1 to 1 on the basis of variables described in the results section and are also presented in Table 2. Logistic regression analyses were then performed to determine whether gender was associated with post-operative mortality as well as secondary outcomes. All the p values described are two-sided and a p value < 0.05 was considered statistically significant.

3. Results

Of the total 13,115 patients who underwent CABG surgery during the study period, 9848 (75.1%) individuals were men. Table 1 compares pre-operative characteristics of these patients. Women were older compared to men and had a higher prevalence of hypertension, diabetes mellitus (including insulin dependent diabetes mellitus), PAD, history of CHF and cerebrovascular disease or TIA. On the other hand, men had a higher proportion of active smokers and had higher proportion of patients with low LVEF and pre-operative aspirin use. At hospital admission, a higher proportion of women had unstable angina, New York Heart Association (NYHA) functional class III or IV

Table 1
Preoperative characteristics of male and female patients undergoing isolated coronary artery bypass grafting.

Variable	Males	Females	p
N (%)	9848 (75.1)	3267 (24.9)	
Mean BMI ± SD[a]	28.7 ± 4.7	28.7 ± 6.1	0.157
Mean age (years) ± SD[a]	62.4 ± 10.2	65.4 ± 10.7	<0.0001
Hypertension, n (%)	7389 (75.0)	2684 (82.2)	<0.0001
Diabetes mellitus, n (%)	3290 (33.4)	1458 (44.6)	<0.0001
Insulin-dependent DM, n (%)	772 (7.8)	526 (16.1)	<0.0001
Unstable angina, n (%)	5008 (50.9)	1875 (57.4)	<0.0001
Low left ventricular ejection fraction, n (%)	3313 (33.6)	930 (28.5)	<0.0001
NYHA Class III and IV, n (%)	7330 (74.4)	2565 (78.5)	<0.0001
Previous MI, n (%)	4191 (42.6)	1356 (41.5)	0.29
Pre-operative renal insufficiency, n (%)	1418(14.4)	492 (15.1)	0.35
Smoking, n (%)	5433 (55.2)	1299 (39.8)	<0.0001
Family history of coronary artery disease, n (%)	3613 (36.7)	1206 (36.9)	0.82
Peripheral vascular disease, n (%)	1711 (17.4)	801 (24.5)	<0.0001
Previous transient ischemic attack, n (%)	295 (3.0)	181 (5.5)	<0.0001
Previous cerebrovascular accident, n (%)	550 (5.6)	299 (9.2)	<0.0001
History of congestive heart failure, n (%)	1558 (15.8)	800 (24.5)	<0.0001
Preoperative intra-aortic balloon pump, n (%)	442 (4.5)	155 (4.7)	0.542
Urgent surgery, n (%)	1932 (19.6)	787 (24.1)	<0.0001
Preoperative aspirin, n (%)	6453 (66.0)	1952 (60.1)	<0.0001
Extent of CAD			<0.0001
Single vessel CAD	1355 (13.8)	681 (20.8)	
Two vessel CAD	2679 (27.2)	874 (26.8)	
Triple vessel CAD	5814 (59.0)	1712 (52.4)	

BMI = Body Mass Index, DM = Diabetes Mellitus, NYHA = New York Heart Association Functional Class, MI = Myocardial Infarction, CAD = Coronary Artery Disease.
[a] SD = standard deviation.

Table 2
Preoperative characteristics of male and female patients undergoing isolated coronary artery bypass grafting after propensity matching.

Variable	Gender		p
	Males	Females	
N (%)	1800 (50.0)	1800 (50.0)	
Age > 65 years, n (%)	931 (52.7)	925 (51.4)	0.841
Obesity (BMI ≥ 30 kg/m^2), n(%)	614 (34.1)	617 (34.3)	0.916
Hypertension, n (%)	1476 (82.0)	1465 (81.4)	0.635
Insulin-dependent DM, n (%)	112 (6.2)	115 (6.4)	0.837
Unstable angina, n (%)	1017 (56.5)	1025 (56.9)	0.788
NYHA Class III and IV, n (%)	1480 (82.2)	1481 (82.3)	0.965
Previous MI, n (%)	694 (38.6)	694 (38.6)	1.000
Pre-operative renal insufficiency, n (%)	120 (6.7)	123 (6.8)	0.842
Smoking, n (%)	744 (41.3)	762 (42.3)	0.543
Peripheral vascular disease, n (%)	233 (12.9)	235 (13.1)	0.921
Previous transient ischemic attack, n (%)	20 (1.1)	25 (1.4)	0.453
Previous cerebro-vascular accident, n (%)	45 (2.5)	44 (2.4)	0.914
History of congestive heart failure, n (%)	243 (13.5)	244 (13.6)	0.961
Preoperative intra-aortic balloon pump, n (%)	66 (3.7)	73 (4.1)	0.544
Urgent surgery, n (%)	308 (17.1)	322 (17.9)	0.539
Preoperative aspirin, n (%)	1152 (64.0)	1152 (64.0)	1.000

BMI = Body Mass Index, DM = Diabetes Mellitus, NYHA = New York Heart Association Functional Class, MI = Myocardial Infarction.

symptoms and required urgent surgery more often than men. A higher proportion of women had single vessel CAD while men had a higher proportion of triple vessel CAD (p-value for trend<0.001). Internal mammary artery was used less often in women compared with men (85.4% vs. 92.3%, p<0.001). Women had an overall shorter cardiopulmonary bypass time (64.9 ± 34.1 vs. 69.3 ± 34.1 min, p<0.0001) and aortic clamp time (37.4 ± 21.6 vs. 40.3 ± 21.7 min, p<0.0001) compared to men.

Table 2 provides baseline demographic and co-morbid variables of interest after propensity score matching. The variables matched using propensity score matching included: old age (>65 years), obesity (BMI ≥ 30 kg/m^2), hypertension, diabetes mellitus (including insulin dependent diabetes mellitus), unstable angina, pre-operative NYHA class III or IV, previous MI, pre-operative renal insufficiency, smoking, PAD, previous transient ischemic attack (TIA), previous stroke, history of CHF, pre-operative use of intra-operative balloon pump (IABP), urgent surgery and pre-operative aspirin use. Our propensity score matching for these variables yielded a total of 3600 patients (n = 1800 in each group).

A total of 448 patients died during the index hospitalization. There were 264/9848 (2.7%) deaths in men compared to 184/3267 (5.6%) deaths in women. Table 3 provides results of unmatched multivariate logistic regression analyses and propensity score matched regression analyses for predictors of post-operative mortality. Female gender [odds ratio(OR) 1.67, 95% confidence interval (CI) 1.35–2.05], old age (OR 1.99, 95% CI 1.61–2.48), urgent or emergent surgery (OR 2.12, 95% CI 1.71–2.63) and pre-operative co-morbidities [renal insufficiency (OR 2.07, 95% CI (1.65–2.60)), prior history of CHF (OR 1.69, 95% CI 1.33–2.14), need for IABP (OR 3.17, 95% CI 2.38–4.22) and prior MI (OR 1.38, 95% CI 1.12–1.71) were all associated with significantly increased risk of post-operative mortality in the unmatched analysis. After propensity score matching, female gender remained an independent predictor associated with higher post-CABG mortality (OR 1.84, 95% CI 1.22–2.78).

Table 3
Predictors associated with post-operative mortality after multivariate stepwise regression analyses and propensity score matched analyses in male and female patients undergoing isolated CABG.

Outcome (mortality)	Multivariate regression analyses	After propensity score matching
	OR (95% CI)[a]	OR (95% CI)[a]
Female gender[b]	1.67 (1.35–2.05)	1.84 (1.22–2.78)
Age >65 years	1.99 (1.61–2.48)	1.92 (1.26–2.93)
Urgent or emergent surgery	2.12 (1.71–2.63)	2.01 (1.29–3.13)
Pre-operative renal insufficiency	2.07 (1.65–2.60)	2.76 (1.62–4.70)
Pre-operative congestive heart failure	1.69 (1.33–2.14)	2.08 (1.32–3.28)
Pre-operative intra-aortic balloon pump use	3.17 (2.38–4.22)	3.88 (2.18–6.89)
Prior myocardial infarction	1.38 (1.12–1.71)	1.60 (1.05–2.44)

[a] Odds ratio, 95% confidence interval.
[b] Male gender used a referent.

The association between gender and secondary outcomes are described in Table 4. In multivariate regression analyses before propensity score matching, female gender was significantly associated with increased odds of post-operative leg wound infections (OR 1.75, 95% CI 1.36–2.54), post-operative stroke (OR 1.37, 95% CI 1.08–1.73) and lower odds for post-operative AF (OR 0.78, 95% CI 0.70–0.86) and the need for re-operation for post-operative bleeding complications (OR 0.78, 95% CI 0.64–0.95). Female gender remained significantly associated with lower rates of post-operative AF (OR 0.76, 95% CI 0.65–0.90) in analyses performed after propensity score matching. The differences in clinical outcomes of post-operative leg wound infection, post-operative stroke and re-operative for bleeding did not show any difference after propensity score matched analysis. Although gender was not associated with post-operative sepsis in multivariate regression analysis before propensity score matching (OR 0.85; 95% CI 0.62–1.15), we did observe a trend towards a lower risk of post-operative sepsis in women (OR 0.57; 95% CI 0.32–1.00). Gender was not associated with post-operative ventilator dependence, post-operative ventricular tachycardia, sternal wound infection, post-operative renal insufficiency, post-operative MI and post-operative bleeding on either multivariate regression analyses or propensity score matched analyses.

Women also had longer length of hospitalization after CABG compared to men (11.9 ± 9.0 days vs. 10.4 ± 9.2 days, p<0.0001).

4. Discussion

We found that female gender is independently associated with an increased risk of in-hospital mortality after isolated CABG surgery after both multivariate regression analyses as well as propensity score matched analyses. Female gender was also associated with a decrease in the risk of post-operative AF and a trend towards lower risk of post-operative sepsis. On the other hand, we did not find any differences in other major post-operative complications including prolonged mechanical ventilation, surgical site infections, ventricular arrhythmia, stroke, renal failure, MI and bleeding. Female patients undergoing CABG on average had a longer length of hospitalization compared with male patients undergoing isolated CABG surgery.

Our finding of higher post-operative mortality in women after isolated CABG is concordant with prior studies reporting post-operative outcomes in women after isolated CABG [1,2,6,7,13,14,16,18,19]. There are however, a few other studies reporting no impact of gender on post-operative mortality despite multivariate analysis with or without propensity matching [1,6,7,12,16,17,20,21]. In agreement with previous studies, our study population at baseline showed higher co-morbid conditions in women including older age, hypertension, diabetes mellitus, CHF, PAD, prior stroke or TIA [1,4,7,16,20,22–26]. In the settings of these major differences in baseline characteristics, a strict propensity matching analysis (selecting only 27.4% of the initial patient population) continued to show the higher post-operative mortality in our study as well as in other similar studies [14,16,18].

Clinical presentation and severity of CAD is influenced by several gender-specific risk factors in women including older age at presentation, more frequent presentation with unstable angina, higher need for urgent interventions, higher pre-operative use of IABP, CHF, prior coronary interventions, diabetes mellitus, hypertension and PAD. [4,14,23–26] Although some of these factors may be more important determinants of post-operative morbidity and mortality

Table 4
Associations of female gender with postoperative secondary outcomes in patients undergoing isolated CABG[a].

Outcome	Males N (%)	Females N (%)	Multivariate regression analyses OR (95% CI)[b]	After propensity score matching OR (95% CI)[a]
Post-operative ventilator dependence	469 (4.8)	222 (6.8)	1.15 (0.96–1.38)	1.21 (0.85–1.72)
Post-operative atrial fibrillation	2175 (22.1)	692 (21.2)	0.78 (0.70–0.86)	0.76 (0.65–0.90)
Post-operative ventricular fibrillation	383 (3.9)	152 (4.7)	1.02 (0.83–1.24)	0.77 (0.53–1.13)
Post-operative ventricular tachycardia	688 (7.0)	227 (6.9)	0.88 (0.75–1.04)	0.79 (0.59–1.06)
Post-operative sepsis	174 (1.8)	63 (1.9)	0.85 (0.62–1.15)	0.57 (0.32–1.00)
Sternal wound infection	491 (5.0)	169 (5.2)	0.88 (0.73–1.07)	1.17 (0.84–1.63)
Leg wound infection	169 (1.7)	112 (3.4)	1.75 (1.36–2.54)	1.52 (0.96–2.42)
Post-operative renal insufficiency	801 (8.1)	320 (9.8)	0.88 (0.76–1.03)	0.90 (0.68–1.20)
Post-operative stroke	224 (2.3)	123 (3.8)	1.37 (1.08–1.73)	1.42 (0.92–2.21)
Post-operative myocardial infarction	343 (3.5)	123 (3.8)	1.02 (0.82–1.27)	0.73 (0.51–1.06)
Post-operative bleeding	1404 (14.3)	538 (16.5)	1.04 (0.92–1.17)	1.05 (0.86–1.29)
Need for re-operation for bleeding	474 (4.8)	136 (4.2)	0.78 (0.64–0.95)	0.72 (0.51–1.02)

[a] Male gender used a referent.
[b] Odds ratio, 95% confidence interval.

than gender itself [27–29], it is important to note that female gender continued to be an independent predictor of increased mortality following CABG despite adjusting for these important covariates.

The issue of higher post-operative mortality in women has been addressed by several hypotheses. These hypotheses include disparity in baseline risk factors as evident in our study as well as reported in various other reports in the past [1,2,4,6,7,14,16–18,22–26,30–34]. We found women to be older and have higher proportion of hypertension, diabetes mellitus, low LVEF, prior peripheral and cerebrovascular arterial disease. Similar findings have been reported elsewhere as well [1,3–5,7,16,23,26,31,32]. Women account for a higher preponderance for metabolic syndrome [14] which may also contribute to adverse outcomes in the post-operative period. Other possible reasons for higher post-operative mortality include delayed presentation due to referral bias and therefore presentation with lower NYHA functional class [6,7,34,35] and higher need for urgent surgical revascularization procedures [6].

Women tend to have smaller body surface area (BSA). Several reports have linked smaller BSA in women to adverse post-operative outcomes [1,2,6,7,14,17,21,33,34,36,37]. The smaller body surface area in general has been linked to worse post-operative outcomes including several-folds increase in mortality regardless of gender [13] in patients with BSA of $<1.6\ m^2$ [38]. A smaller BSA in women correlates with a smaller diameter of epicardial coronary arteries potentially increasing risk of future adverse outcomes due to poor graft patency [1,13,21,28,37]. On the same note, a smaller BSA in women can be related to intra-operative hemodilution requiring platelet products and plasma transfusions both being risk factors for increased morbidity and mortality in the peri-operative period [37].

Women tend to receive a lower proportion of arterial grafts especially internal mammary artery (IMA) graft to left anterior descending (LAD) artery. This was seen in our study and has also been reported in the past. [1,16,17,28,34] This may be one of the potential explanations for increased mortality as well.

It is important to note despite adjusting for all these factors gender based differences, female gender was associated with an increase in post-operative mortality in our multivariate regression analyses as well as propensity score matched analyses. This could be due to the fact that there could be other differences between males and females that we did not use in adjustment models or did not match for but more importantly, these differences reflect unknown or unmeasured confounding.

In our baseline un-adjusted analyses, women had higher odds for post-operative complications including surgical site infection and post-operative stroke. However after propensity score matched analysis, these differences were no longer significant. Similarly, we observed a trend towards lower risk of post-operative sepsis in women but this difference was not significant. Several reports have shown increased post-operative morbidity in women after isolated CABG including stroke [16], post-operative MI, prolonged mechanical ventilation [16,17], prolonged intensive care unit (ICU) stay requiring vasopressor support [11,12,14] as well as respiratory failure, surgical site infections (especially deep sternal wound infections) and sepsis [17]. Multiple factors could explain differences in our post-operative outcomes compared to prior reports including a strict propensity score matching (3600/13,115, 27.4% sample) resulting in removal of referral bias and correction of baseline differences. Secondly, this report presents data from a high volume tertiary care referral center and therefore operator experience and post-operative critical care may also partially explain similar outcomes for various morbidity outcomes between the two genders. In-hospital post-operative stroke has not traditionally been related to gender and it is confirmed in our matched analysis as well. [17,34].

We also found lower risk of post-operative AF in women despite propensity score matching analysis. Our findings are consistent with previously reported higher risk of post-operative AF in males [39–41]. This increased post-operative AF in males could be related to clinical or subclinical heightened inflammatory state including elevated interleukin-6 and c-reactive protein levels in the setting of prolonged cardiopulmonary bypass times as evidenced in our study as well as reported by other authors [42,43].

Our study has limitations. It represents the experience of a single, tertiary care referral center which may be affected by referral bias. We performed propensity score matched analysis to control for possible referral bias. Only 27.4% (3600/13,115) of the initial patient population were used in propensity matched analysis. The two groups of patients were different on several variables (Table 1) with women being generally sicker as compared to men. We attempted to correct for these differences using stepwise multivariate logistic regression model and propensity score matching. Although these analyses in general are robust, there could be incomplete adjustment for variables that we did not account for. In addition, both multivariate logistic regression analyses and propensity score matched analyses in general do not account for unmeasured confounding. Other limitations inherent to retrospective chart review include possibility of incomplete data capture and a dependency on previously recorded data in the medical records, whose quality may be limited by systematic or recorder bias. However, the use of trained chart abstractors with written definition of each variable as well as outcome and a large patient population in our analysis may reduce this bias on clinical outcomes. These limitations should be kept in mind while interpreting the clinical outcomes presented in the current analysis.

In this propensity score matched retrospective analysis, female gender was found to be an independent predictor of post-operative mortality. Our findings warrant a higher vigilance in women patients undergoing isolated CABG.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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