Sex differences in outcomes following isolated coronary artery bypass graft surgery in Australian patients: analysis of the Australasian Society of Cardiac and Thoracic Surgeons cardiac surgery database

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Abstract

OBJECTIVES: Women undergoing isolated coronary artery bypass graft (CABG) surgery have been previously shown to be at an independently increased risk for post-operative morbidity and mortality. The current study evaluates the impact of sex as an independent risk factor for early and late morbidity and mortality following isolated CABG surgery.

METHODS: Data obtained between June 2001 and December 2009 by the Australasian Society of Cardiac and Thoracic Surgeons Cardiac Surgery Database Program was retrospectively analysed. Demographic, operative data and post-operative complications were compared between male and female patients using chi-square and t-tests. Long-term survival analysis was performed using Kaplan–Meier survival curves and the log-rank test. Independent risk factors for short- and long-term mortality were identified using binary logistic and Cox regression, respectively.

RESULTS: CABG surgery was undertaken in 21,534 patients at 18 Australian institutions; 22.2% were female. Female patients were generally older (mean age, 68 vs. 65 years, \( P < 0.001 \)) and presented more often with congestive heart failure (\( P < 0.001 \)), hypertension (\( P < 0.001 \)), diabetes mellitus (\( P < 0.001 \)) and cerebrovascular disease (\( P < 0.001 \)). Women demonstrated a greater 30-day mortality (2.2% vs. 1.5%, \( P < 0.001 \)) on univariate analysis but not on multivariate analysis (\( P = 0.638 \)). Similarly, women demonstrated a greater late mortality than men on univariate analysis (\( P = 0.006 \)) but not on multivariate analysis (\( P = 0.093 \)). Women had a decreased risk of early complications including new renal failure (\( P = 0.001 \)) and deep sternal wound infection (\( P = 0.017 \)) but were more likely to require red blood cell transfusion (\( P < 0.001 \)).

CONCLUSIONS: Female patients undergoing isolated CABG surgery have a greater 30-day mortality which may be accounted for by a poorer pre-operative risk factor profile. Further investigation is required into the reasons for differential outcome after CABG based on sex.

Keywords: Cardiac surgery • Coronary artery bypass graft surgery • Gender • Sex • Mortality • Morbidity • Survival

INTRODUCTION

Women who undergo coronary artery bypass grafting (CABG) have been previously shown to be at an increased risk of peri-operative mortality and morbidity when compared with men [1–5]. Numerous explanations for this disparity have been proposed. Some investigations have argued that female sex is independently associated with a poor peri-operative outcome [2, 4]. As such numerous risk models developed to predict the operative mortality associated with CABG have included female gender as a risk factor [6, 7]. Conversely, other investigators have argued that sex differences in outcomes can be largely attributed to co-morbid conditions more prevalent in females such as smaller coronary arteries and underutilization of arterial grafts [8–13]. Moreover, almost all studies have demonstrated that women are older at time of surgery, present at a more acute and symptomatic stage of disease and have a higher incidence of congestive heart failure and diabetes. These factors have been consistently associated with a poor outcome and confound any comparison between men and women.

Given the association of female sex with a poor peri-operative outcome, many clinicians have adopted a cautious approach...
towards the management of women with coronary artery disease [9]. As such concerns are being raised that the perception of a worse outcome after CABG in women has resulted in a delayed treatment of women with coronary artery disease which has increased peri-operative mortality and morbidity and accentuated any real differences that may exist [9]. Due to the need for increased understanding of the disparity in outcomes between men and women, we evaluated contemporary data on gender outcomes following isolated CABG using the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) Cardiac Surgery Database. The aim is to increase understanding on this important issue by adjusting for the relevant confounding patient and treatment-related factors.

PATIENTS AND METHODS

All patients undergoing isolated CABG between 1 June 2001 and 31 December 2009, at hospitals in Australia participating in the ASCTS Cardiac Surgery Database were included in this study. Patients having concomitant valve surgery or other concurrent cardiac surgical procedures were excluded from this study. All six Victorian public hospitals that which perform adult cardiac surgery—The Royal Melbourne Hospital, The Alfred Hospital, Monash Medical Centre, The Geelong Hospital, Austin Hospital and St Vincent’s Hospital Melbourne—were involved in the prospective data collection during the entire period. Additionally, 14 cardiac surgical units from South Australia, New South Wales and Queensland have entered the database project in the last 30 months of the study period and contributed 42.4% of the total patient numbers. Given the fact that 14 interstate hospitals have started to contribute patients only within the last 1–2.5 years, a greater number of Victorian interstate patients have been accumulated so far compared with interstate patients.

The ASCTS database contained detailed information on patient demographics, pre-operative risk factors, operative details, post-operative hospital course and morbidity and mortality outcomes. These data were collected prospectively using a standardized data set and definitions. Data collection and audit methods have been previously described [14]. In the State of Victoria, the collection and reporting of public hospital cardiac surgery data is compulsory and mandated by the State Government; hence it is all-inclusive. Data validation has been a major focus since the establishment of the ASCTS database. The data are subjected to both local validation and an external data quality audit program, which is performed on site to evaluate the completeness (defined as <1% missing data for any variable) and accuracy (97.4%) of the data held in the combined database. Audit outcomes are used to assist in further development of appropriate standards. The Ethics Committee of each participating hospital had previously approved the use of de-identified patient data contained within the database for research and waived the need for individual patient consent.

For the purpose of this study, patients were divided into two groups on the basis of their sex. Pre-operative characteristics, early outcomes and long-term survival were compared between the two groups.

Fourteen early post-operative outcomes were analysed. These are: (a) 30-day mortality, defined as death within 30 days of operation; (b) permanent stroke, defined as a new central neurological deficit persisting for >72 h; (c) transient stroke, defined as a new transient neurological deficit that resolves completely within 72 h (transient ischaemic attack or reversible ischaemic neurological deficit); (d) post-operative acute myocardial infarction, defined as at least two of the following: enzyme-level elevation, new cardiac wall motion abnormalities or new Q waves on serial electrocardiograms; (e) new renal failure, defined as at least two of the following: serum creatinine increased to more than 200 µmol/l, doubling or greater increase in creatinine vs. pre-operative value or new requirement for dialysis or hemofiltration; (f) prolonged ventilation (>24 h); (g) multi-system failure, defined as the concurrent failure of two or more of the cardiac, respiratory or renal systems for at least 48 h; (h) red blood cell transfusion; (i) gastrointestinal (GI) complications; defined as post-operative occurrence of any GI complication; (j) deep sternal infection involving muscle and bone as demonstrated by surgical exploration and one of the following: positive cultures or treatment with antibiotics; (k) return to the operating theatre for any cause; (l) return to the operating theatre for bleeding and (m) in-hospital mortality, defined as death during hospital stay.

To assess the role of sex for each early outcome, logistic regression analysis was used to adjust for 20 pre-operative patient variables, with the outcome as the dependent variable (variables in Table 4). A Hosmer–Lemeshow test was applied to assess the goodness-of-fit of the 30-day mortality and in-hospital mortality models. Long-term survival status was obtained from the Australian National Death Index. The closing date was 18 March 2010. A Kaplan–Meier estimate of survival was obtained. Differences in long-term survival were assessed by the log-rank test. The role of sex in long-term survival was assessed by constructing a Cox proportional hazards model using sex and other pre-operative patient characteristics as variables. Continuous variables are presented as mean ± one standard deviation. The Mann–Whitney U-test was used to compare two groups of continuous variables. The chi-square test was used to compare groups of categoric variables. All calculated values of P were two-sided, and P < 0.05 was considered significant. Statistical analysis was performed using SPSS® for Windows version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient demographics and pre-operative variables

CABG surgery was undertaken in 21 534 patients at 18 Australian institutions; 4780 (22.2%) were female. Pre-operative and demographic characteristics of male and female patients are provided in Table 1. Female patients were older and were more likely to present with chronic obstructive pulmonary disease, diabetes mellitus, hypercholesterolaemia, hypertension, cerebrovascular disease, congestive heart failure and unstable angina. They were less likely to have an impaired left ventricular ejection fraction but were more likely to have marked or severe symptoms from their heart disease (NYHA class III or IV). The incidence of a previous myocardial infarction and triple vessel disease was lower in women. Women were more likely to undergo an urgent or emergency procedure compared with men. The mean body surface area of women was significantly lower than men.

Intra-operative data

There were some differences in intra-operative variables between the two groups and they are documented in Table 2.
The use of off-pump techniques was higher in women. There was a decreased mean number of distal anastomoses in women. Women had fewer distal coronary anastomoses than men and, consequently, shorter bypass and cross-clamp times. The use of internal mammary artery graft and radial artery graft was significantly lower in women.
Early outcomes

Significant differences between the groups were documented in early post-operative outcome (Table 3). Overall 30-day mortality and in-hospital mortality were 1.6 and 1.8%, respectively. The unadjusted 30-day mortality rate was 2.2% in women and 1.4% in men. This difference was significant on univariate analysis ($P = 0.001$) but not on multivariate analysis ($P = 0.765$). Table 5 summarizes the logistic regression model predicting in-hospital mortality.

After adjustment for differences in all patient variables, female gender was protective for complications such as new renal failure, deep sternal wound infection, sepsisemia, multi-system failure, return to theatre and return to theatre for bleeding. However, females were more likely to require red blood cell transfusion than males. On univariate analysis, females had a significantly higher mean post-operative length of stay (9.39 ± 8.8 vs. 8.5 ± 9.2 days, $P < 0.001$) but not intensive care unit stay (45.59 ± 149.33 vs. 43.45 ± 75.27 h, $P = 0.177$) compared with males.
Late outcomes

Long-term survival at 3 months and 1, 3, 5 and 7 years post-operatively was significantly lower in women compared with men on univariate analysis (97.2 vs. 98.2%, 95.9 vs. 97.0%, 92.9 vs. 94.1%, 88.2 vs. 89.2% and 82.8 vs. 84.1%, \( P = 0.006 \)) (Fig. 1). After adjusting for differences in patient variables, female sex was not independently associated with long-term survival (\( P = 0.093 \)). A univariate Cox regression model summarizing late mortality is summarized in Table 4. A multivariate Cox regression model predicting late mortality is summarized in Table 5.

**DISCUSSION**

The incidence of operative mortality and other peri-operative complications have been consistently shown to be higher in women, compared with men [1-4]. Some investigators have argued that this reflects an independent association between female gender and a poor peri-operative outcome [2, 4]. Of the numerous risk models which have been developed to predict operative mortality, several including EuroSCORE have included female sex as a negative prognostic factor [6, 7, 15, 16]. Recently, Bukkapatnam et al. [4] compared the outcomes of 10,708 women and 29,669 men who underwent isolated CABG in 2003–04. They demonstrated on multivariate analysis that women were at higher risk for operative mortality than men (HR 1.61; 95% CI 1.41–1.84; \( P < 0.001 \)). An earlier study by Edwards et al. [1] analysed the data from 247,760 men and 97,153 women from the Society of Thoracic Surgeons National Cardiac Surgery database and demonstrated that female gender was an independent predictor of post-operative death within most defined risk groups.

Other investigators have instead argued that female sex is not independently associated with higher operative mortality once confounding factors are taken into account [8-11]. Koch et al. [8] performed a propensity analysis and demonstrated that the pre-operative profiles of women and men were markedly different. In well-matched patients, however, female sex was not associated with increased mortality and had a minimal impact on morbidity after CABG. Unfortunately, 74% of women in the cohort were excluded because they could not be matched limiting the generalizability of these results. It is important to note that most studies have incorporated different variables in the analysis. As such, the parameterization of the different models is not directly comparable. Moreover, the methods of statistical

### Table 5: Multivariate predictors for 30-day, in-hospital mortality and late mortality in entire cohort (n = 21534)

<table>
<thead>
<tr>
<th>Pre-operative variables</th>
<th>30-day mortality</th>
<th>In-hospital mortality</th>
<th>Late mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>P-value</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.03–1.06)</td>
<td>&lt;0.001</td>
<td>1.05 (1.03–1.06)</td>
</tr>
<tr>
<td>Female</td>
<td>0.93 (0.68–1.27)</td>
<td>0.638</td>
<td>0.96 (0.71–1.29)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.06 (0.77–1.45)</td>
<td>0.727</td>
<td>1.23 (0.92–1.64)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.00 (0.61–1.07)</td>
<td>0.984</td>
<td>1.17 (0.92–1.64)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.81 (0.61–1.07)</td>
<td>0.134</td>
<td>0.91 (0.69–1.20)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.26 (0.91–1.74)</td>
<td>0.164</td>
<td>1.29 (0.94–1.77)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.83 (0.59–1.17)</td>
<td>0.282</td>
<td>1.09 (0.80–1.47)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.37 (1.02–1.84)</td>
<td>0.037</td>
<td>1.28 (0.96–1.69)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.80 (1.19–2.71)</td>
<td>0.005</td>
<td>1.72 (1.15–2.56)</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.28 (0.94–1.74)</td>
<td>0.113</td>
<td>1.21 (0.90–1.62)</td>
</tr>
<tr>
<td>Recent myocardial infarction (&lt;21 days)</td>
<td>1.53 (1.16–2.02)</td>
<td>0.002</td>
<td>1.59 (1.22–2.08)</td>
</tr>
<tr>
<td>History of congestive heart failure (%)</td>
<td>1.91 (1.45–2.52)</td>
<td>&lt;0.001</td>
<td>1.82 (1.40–2.37)</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>1.52 (1.12–2.07)</td>
<td>0.007</td>
<td>1.52 (1.13–2.05)</td>
</tr>
<tr>
<td>Left main stenosis &gt; 50%</td>
<td>1.30 (1.01–1.67)</td>
<td>0.040</td>
<td>1.39 (1.09–1.76)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 0.45</td>
<td>1.99 (1.52–2.59)</td>
<td>&lt;0.001</td>
<td>2.08 (1.61–2.68)</td>
</tr>
<tr>
<td>New York Heart Association classification III or IV</td>
<td>1.41 (1.09–1.84)</td>
<td>0.010</td>
<td>1.35 (1.05–1.74)</td>
</tr>
<tr>
<td>Triple vessel disease</td>
<td>1.17 (0.86–1.59)</td>
<td>0.330</td>
<td>1.14 (0.85–1.54)</td>
</tr>
<tr>
<td>Non-elective procedure</td>
<td>1.60 (1.18–2.17)</td>
<td>0.002</td>
<td>1.41 (1.05–1.87)</td>
</tr>
<tr>
<td>Critical pre-operative state</td>
<td>2.54 (1.88–3.43)</td>
<td>&lt;0.001</td>
<td>2.62 (1.96–3.50)</td>
</tr>
<tr>
<td>Body surface area</td>
<td>0.33 (0.16–0.68)</td>
<td>0.003</td>
<td>0.42 (0.21–0.84)</td>
</tr>
</tbody>
</table>

**Figure 1:** The overall survival of patients after CABG surgery, stratified by sex.
analysis vary between studies. Bukkapatnam et al. [4] applied logistic regression techniques incorporating 25 variables. Unique data not analysed in this study including pre-operative hepatic disease and race were incorporated in the analysis, although body surface area was not included. Koch et al. [8] constructed a propensity model by accounting for 74 pre-operative variables with detailed data on pre-operative medication, laboratory values and body surface area. As stated earlier, female gender was not a negative prognostic indicator. It is possible, therefore, that in models where female sex remained valid as an independent predictor of a worse outcome that insufficient information was available for correction of variability.

Our contemporary analysis of 21,534 patients, including 4780 women, demonstrated a higher rate of 30-day mortality in women, compared with men on univariate analysis (2.2 vs. 1.4%; HR 1.54; 95% CI 1.22–1.94; P < 0.001). After adjusting for confounding factors, however, this disparity did not exist (HR 0.93; 95% CI 0.68–1.27; P = 0.638). The strength of our model is demonstrated by the fact that the Hosmer–Lemeshow χ² statistic is 2.46 with P = 0.96 implying an excellent fit. As such our data suggest that co-morbid factors more prevalent in females rather than female gender itself are associated with the significantly poorer outcome. A comparison of the pre-operative characteristics between men and women highlights the significant disparities between them. Female patients, on average, were 4 years older and presented more often with chronic respiratory disease, diabetes, hypertension, cerebrovascular disease, congestive heart failure and NYHA class III/IV. Moreover, women more often required an urgent intervention which is likely to reflect a more acute and unstable presentation. These findings are consistent with the published literature and suggest that any direct comparison between men and women is inherently prejudicial [2, 4, 10, 12]. Importantly, and perhaps expectedly, women had a significantly lower body surface area compared with men. This factor, often excluded in analysis comparing men and women, may reflect coronary artery size. Smaller coronary arteries have a smaller margin for error and therefore more likely to fail in the post-operative period. Several investigators have argued that this factor contributes to gender-related disparity [10, 12], although not all have agreed [1, 2]. Given that our study showed an independent association of a low body surface area with 30-day mortality, our data support the former hypothesis.

There were also differences in the intra-operative profiles between men and women. Women received fewer arterial grafts and less extensive revascularization with fewer bypasses. This finding is consistent with previous studies which have shown lower rates of arterial, specifically internal thoracic artery (IMA) use than men [1, 17, 18], even after adjustment for other factors such as age, non-elective surgery and extent of disease [9, 17]. Aldea et al. [9] in a multivariate analysis demonstrated that female gender was independently associated with a decreased use of the IMA graft. Since arterial grafts have higher patency rates than saphenous vein grafts [19], it has been proposed that the lower use of IMAs in women could be a potential mediator of gender differences in outcomes. However, the independent relationship of IMA with early mortality is inconsistent with some CABG series demonstrating an association with increased mortality [11, 17, 18] and others finding none [1, 9, 20]. In the current series, IMA graft use was demonstrated to be less prevalent in females. The use of IMA grafting in women in our series, however, is significantly higher than most studies that have been previously reported (60–85%), including a 65.3% incidence reported by the national STS database for 1994–1996 [1]. Disparities in the use of radial artery grafts have received more attention in recent years. Lawton et al. [21] demonstrated in a series of 2633 patients that the use of radial artery was only 35% in women compared with 44% in men. Radial artery use was actually associated with superior long-term survival in all patients. Cohen et al. meanwhile demonstrated that radial artery use was independently associated with a lower incidence of early mortality and morbidity [22]. In our series 59.5% of male patients received a radial graft compared with 53.5% of females. Therefore, our contemporary data conform to the published literature and indicate that women continue to receive less arterial conduits than men and this may contribute to higher rate of 30-day mortality, although further evidence is required.

Encouragingly, female gender was not associated with an increase in most procedure-related complications. In fact, female gender was independently associated with a reduced risk of new renal failure, deep sternal wound infection, septicaemia, return to theatre and return to theatre for bleeding. The fact that female gender is not associated with a decline in renal function after CABG surgery has been recently demonstrated [23]. The lower incidence of deep sternal wound infection may be attributed to the lower use of right internal mammary artery graft in women but this requires further investigation. It is also possible that women get fewer distal anastomoses related to poorer graft material, although an assessment of graft quality is not possible with our manuscript. This topic merits also further investigation. However, red blood cell transfusion was more frequently required in females and the overall length of hospital stay was longer. Aldea et al. [9] demonstrated that the incidence of major complications was not significantly different between men and women, although women were more likely to require RBC transfusion. Given than allogenic blood transfusion is an important predictor for time to extubation, post-operative complications and length of hospital stay [24], several investigators have proposed cell saving techniques to minimize transfusion in women, who are generally more anaemic at the time of presentation and because of smaller size, may be more prone to haemodilution [9]. Although these techniques have been widely applied in high risk groups, their general applicability in women undergoing CABG requires further investigation.

Long-term survival was higher in men compared with women on univariate analysis (HR 1.15; 95% CI 1.04–1.28; P = 0.005) but not on multivariate analysis (HR 0.90; 95% CI 0.79–1.02; P = 0.093). Our data demonstrated a lower 3-month survival in women compared with men (97.2% vs. 98.2%). The survival difference at 7 years was similar (82.8 vs. 84.1%), implying that female sex does not portend a poor prognosis after an initial period of increased mortality. Again, it is likely that co-morbid and treatment-related factors as described above contribute to the disparity in overall survival between the two groups. Given that our data indicate that women are not more prone to infection after CABG, in fact they were shown to be less susceptible, a more aggressive effort to afford women complete revascularization should be offered to ensure long-term outcomes equivalent to those in men.

This study has significant strengths and weaknesses. This large, contemporary study from a robustly validated multi-institutional database is likely to reflect real world practice reasonably accurately. The main limitation is that it is a retrospective review, and although capturing all surgical patients, there is potential selection bias which would have precluded a fair comparison
between men and women. The retrospective nature of the database also does not allow us to answer several questions. For example, the retrospective nature of our database does not allow us to determine the reason why there is no difference in the incidence of 30-day mortality in females even though the rate of many complications was lower. Similarly, because of the retrospective nature of the ASCTS database, we are unable to determine why the reoperation rate for bleeding was lower in women despite a higher incidence of blood transfusion. Another limitation of this study, and of other database analysis studies, is that many continuous variables are presented as dichotomous variables. For example, ejection fraction and left main disease >50% were presented as dichotomous variables. This limitation, shared with similar studies, reduces the power of our study. We did analyse some variables, including age and body surface area as continuous variables. A previous study analysing the independence of patient variables employed a rich set of continuous variables which would be useful in this case [25]. Nevertheless, as previously stated, the Hosmer–Lemeshow statistic of the current study is 0.96 implying an excellent fit.

Several further investigations are necessary to verify our data. First, confirmatory analysis using a contemporary, international database is imperative to validate the findings from our study. This would particularly be the case if a similar set of variables and modelling techniques applied in this study were used. Alternatively, propensity-based matching statistics adjusting for confounding variables could be useful. Moreover, a prospective investigation with clearly defined outcomes and variable would be useful.

In conclusion, our study demonstrates that the disparity in short- and long-term mortality between men and women can be largely explained by differences in patient demographics and treatment-related factors. Female patients are more likely to present at an older age, with multiple co-morbidities (respiratory disease, diabetes, peripheral vascular disease, renal failure, congestive heart failure) and a more acute presentation. Our analysis strongly suggests that these factors, more prevalent in women, predispose women to a higher incidence of early and late mortality. Although further investigation is required to clarify differences between men and women, these data encourage us to suggest that female gender is not independently associated with poorer outcomes.

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