Higher mortality in women undergoing coronary artery bypass grafting

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Abstract

Aims While men have higher rates of cardiovascular disease, several studies report women having higher mortality after cardiac surgery, reasons for which are unclear. We compared characteristics and outcomes of coronary artery bypass grafting (CABG) by sex.

Methods All patients undergoing isolated CABG during July 2010–June 2012 were grouped by sex for retrospective analyses.

Results A total of 168 (20.5%) women and 650 (79.4%) men were included, followed-up for 1.4±0.6 years. Women were older (66.4 vs 64.0 years; p=0.007), with higher body mass index (30.1 vs 28.8 kg/m²; p=0.004), increased prevalence of hypertension (78.9% vs 67.8%; p=0.008), current smoking (20.2% vs 13.1%; p=0.027), chronic respiratory disease (22.6% vs 15.4%; p=0.028) and estimated glomerular filtration rate (74 vs 81 ml/min/1.73m²; p=0.007). Women had less grafts performed (3.1 vs 3.3; p=0.014) and less use of radial grafts (14.9% vs 25.2%; p=0.004). Female sex was independently associated with higher 30-day mortality (4.8% vs 0.8%) odds ratio 5.63, 95% confidence interval 1.67-19.0; p=0.005 and medium-term mortality hazards ratio 2.49, 1.06-5.84; p=0.037 (1-year survival 93.9% vs 98.1%); but not surgical morbidity (21.4% vs 16.9%; p=0.661).

Conclusion Women had higher 30-day and medium-term mortality after CABG even after adjusting for higher prevalence of risk factors and comorbidities.

Ischaemic heart disease (IHD) was the single most common cause of death in New Zealand (NZ) at 19.0% in 2009, with 45.3% being women.¹ Coronary artery bypass grafting (CABG) is the standard treatment for patients with severe three-vessel or left main stem coronary disease, and multi-vessel disease in diabetic patients.²–⁴ Many,⁵–¹⁵ but not all¹⁶–¹⁹ studies have found women to have higher rates of mortality and morbidity after CABG. Most contemporary operative risk scores therefore include sex as an important parameter for predicting mortality after cardiac surgery.²⁰,²¹ However, sex is frequently an underappreciated risk factor in the decision making for CABG and is not included in the New Zealand Access or Urgency Scores. Outcomes according to sex have also not been investigated in a NZ cohort.

We aimed to compare characteristics and mortality and morbidity outcomes by sex in a contemporary cohort of New Zealanders undergoing CABG.

Methods

Ethics—Ethics approval of this study was obtained from our hospital’s Ethics Committee. Consecutive patients having isolated CABG without concomitant valve surgery from July 2010 to June 2012 at
Auckland City Hospital were included in the study. Relevant pre-, peri- and post-operative data were retrospectively collected from computerised clinical records.

**Definitions**—The following definitions were used for baseline characteristics. Angina was graded using the Canadian Cardiovascular Society Classification (CCS) and heart failure by the New York Heart Association Functional Classification (NYHA). Hypertension was defined as prescribed medications for lowering blood pressure, any measurement of over 140/90 mmHg prior to operation or a previous formal diagnosis.

Hypercholesterolaemia referred to total cholesterol >5.0mmol/L, on treatment to lower cholesterol before admission or a previous formal diagnosis. Stroke included any previous history of a neurological deficit that persisted over 24 hours and caused by disturbance of cerebral blood supply. Peripheral vascular disease included claudication, vascular intervention or amputation of peripheries for arterial insufficiency, aortic aneurysm and ankle brachial index <0.9 or imaging evidence of >50% stenosis in any peripheral artery.

Chronic respiratory diseases included use of inhaled corticosteroids for respiratory symptoms, forced expiratory volume in 1 second (FEV1) <80% on spirometry, or previous formal diagnosis. The number of major coronary vessels with >50% stenosis was recorded. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of diet and renal disease equation using the last pre-operative serum creatinine measurement. The operative risk was calculated using logistic EuroSCORE I.

Operative variables collected include number of grafts and duration of cardiopulmonary bypass and aortic cross-clamp. Post-operative high-sensitivity troponin T (hs-TnT) was routinely measured 12-24 hours post-operatively. The development of new Q-waves or left bundle branch block (LBBB) on ECG on day 3 after CABG or new regional wall motion abnormalities on post-operative echocardiogram were independently interpreted by two authors (TKMW and HDW).

Five post-operative complications as defined by the Society of Thoracic Surgeon’s (STS) score and their composite were determined. These included permanent stroke (acute neurological deficit>24 hours due to cerebral blood supply disturbance), renal failure (new dialysis requirement or increase of creatinine to >4.0 mg/dL and ≥3 times last pre-operative level), prolonged ventilation >24 hours, deep sternal wound infection and return to theatre for any reason.

Mortality data were checked against New Zealand’s national registry up till 31 December 2012. Thirty-day mortality, medium-term mortality and composite surgical morbidity were our main pre-specified outcomes.

**Statistical analyses**—Continuous and categorical variables were presented as mean (standard deviation) and percentages (frequency) respectively. Mann-Whitney U test and Fisher’s exact test were used were used for univariate analyses. Univariate survival analysis was performed using Kaplan-Meier curves and log-rank (Mantel-Cox) test.

Multivariate analyses was performed on variables with p<0.10 in univariate analysis. Logistic regression was used to calculate odds ratios (OR) for cross-sectional outcomes and Cox proportional hazards regression used to calculate hazards ratios (HR) for longitudinal outcomes, together with their 95% confidence intervals (95%CI). SPSS (version 17.0, SPSS Inc., Chicago, IL, USA) and Prism (version 5, GraphPad Software, San Diego, CA, USA) software were used for analyses. All tests were two tailed and p-value less than 0.05 were d statistically significant.

**Results**

Out of 818 CABG patients included in the study, 168 (20.5%) were women. Table 1 presents the pre-operative characteristics by sex. Women were older (66.4 vs 64.0 years; p=0.007), had higher body mass index (30.1 vs 28.8 kg/m²; p=0.004), higher CCS class for angina (p=0.037), had higher prevalence of hypertension (78.9% vs 67.8%, p=0.008) and chronic respiratory disease (22.6% vs 15.4%; p=0.028), more were current smokers (20.2% vs 13.1%; p=0.027) and had impaired renal function (74 vs 81 ml/min/1.73m²; p=0.007). Women also had significantly higher logistic EuroSCORE I (6.6% vs 4.0%; p<0.001).
Table 2 presents the operative and post-operative variables by sex. Women had lower number of bypassed vessels (3.1 vs 3.3; p=0.014) and lower proportion who had radial grafts used (14.9% vs 25.2%; p=0.004). Duration of cardiopulmonary bypass and aortic cross-clamp were similar. Women had higher 30-day mortality (4.8% vs 0.8%; p=0.001). Individual and composite surgical morbidities as well as length of hospital stay did not differ by sex.

View Tables 1–3 here

Figure 1. Kaplan-Meier survival curves of isolated coronary artery bypass grafting by sex

Kaplan-Meier survival curves are illustrated in Figure 1, for a mean follow-up of 1.4±0.6 years. Women had higher medium-term mortality during follow-up with hazards ratio 3.88, 95% confidence interval 1.43–10.6, p=0.008, although this appears to be weighted solely from differences within the first 30 days. One-year survival was 93.9% for women and 98.1% for men.

Table 3 presents the predictors of the pre-specified surgical outcomes in multivariate analyses. Female sex was independently associated with 30-day mortality (hazards
ratio 5.63, 95% confidence interval 1.67–19.0, \( p=0.005 \) and medium-term mortality (2.49, 1.06–5.84, \( p=0.037 \)), but not surgical morbidity (\( p=0.661 \)).

**Discussion**

This study shows in a major New Zealand Cardiac Surgery Centre that 30-day and medium-term mortality after CABG was higher in women than men at 6.4 times and 3.9 times respectively. Even after adjusting for other relevant variables in multivariate analysis, the corresponding ratios were 5.6 and 2.5.

Other studies have reported mixed results. Several found female sex to be independently associated with higher early (usually 30-days or in-hospital) and/or late mortality (2–7 years) after CABG with ratios of 1.2–2.3. Some found women to have higher mortality that could be explained by differences in baseline characteristics. Several found no differences in mortality between women and men, and in several women had slightly better late survival.

Women in our cohort had more cardiovascular risk factors and comorbidities than men. Women were older, had higher body mass index, higher CCS class for angina, higher prevalence of hypertension, more chronic respiratory disease and worse renal function. All of these parameters are established predictors of higher mortality after cardiac surgery and are included in the EuroSCORE and/or STS scores. Women had higher EuroSCOREs in our cohort given their sex which is included in the EuroSCORE, older age and more comorbidities, they also had higher STS scores. These are important reasons that at least partially explain the worse outcomes that we found after CABG for women.

Other risk factors found to be more prevalent in women who had CABG reported by at least three studies include higher NYHA class or history of congestive heart failure, hyperlipidaemia, diabetes, peripheral vascular disease, cerebrovascular disease and urgent surgery. We did not find these associations in our cohort which may be because of the lack of power compared to other studies.

Some previous studies have also reported that women having CABG are less likely to be current smokers, have had previous CABG, impaired ejection fractions, and less extensive coronary artery disease. We did not find these associations in our cohort. Indeed we found more women were current smokers than men, putting them at higher risk for both cardiovascular and respiratory diseases. These findings may explain the difference in mortality after CABG by sex was greater in our cohort compared to other studies.

As previously reported, we found women to have less surgical bypass anastomoses and less use of radial grafts. Fewer anastomoses may reflect less extensive coronary artery disease, but also females have smaller coronary arteries than men and target vessels may have been too small to be grafted.

Other studies have also found less utilisation of internal mammary grafts and shorter duration of cardiopulmonary bypass or aortic cross-clamp in women, most likely due to less grafting being performed. Under-utilisation of arterial
grafts which have better patency, inadequate revascularisation as well as longer time on cardiopulmonary bypass are all established predictors of mortality after CABG in women.\(^5,13,17–19,22\)

Despite the differences by sex mentioned above, there may be other characteristics beyond baseline and operative characteristics not accounted for that relate to female sex being independently associated with mortality after CABG. The first group of reasons are characteristics unique to women, including smaller coronary vessels\(^23\) resulting in greater technical difficulty, reduced perfusion and graft failure. Women may also have more coronary microvascular dysfunction,\(^24\) and ovarian oestrogen receptor or ovarian dysfunction.\(^25\) The second category of reasons is related to the presentation and management of women with IHD.\(^26\) Women are more likely to have atypical ischaemic symptoms,\(^27\) silent, unrecognised or late presentation\(^28\) and to receive less aggressive or delayed investigations and interventions.\(^29\) The presence of higher angina class and a trend for higher heart failure class in women in our study suggests that they may have received less aggressive and/or delayed interventions than men. These factors would be expected to lead to worse outcomes after CABG in women.

Only 20.5% of CABG performed in our cohort were in women, even though approximately 45% of IHD deaths in NZ occur in women. Our data show that women are more symptomatic than men prior to CABG, have a higher prevalence of risk factors than men and do worse than men after CABG with higher mortality. There is thus a need to raise the awareness of managing IHD in women in respect of earlier screening, early performance of investigations and referral for CABG as appropriate. The NZ national guidelines recommend cardiovascular risk screening 10 years later in women compared to men and 10 years later than national funding screening for breast cancer (55 vs 45 years of age),\(^30\) even though deaths from IHD are more common than deaths from breast cancer. There should be a lower age threshold for screening for cardiovascular risk factors than the 55 years of age currently recommended and similar to the 45 years of age for men. In addition, the indications for cardiac investigations should take into account the often atypical presentation of women.

**Limitations**—This is a retrospective observational study. The number of patients and pre-specified end-points was limited given that it was a single-centred cohort, so that there was limited statistical power. Follow-up time was restricted as this was a recent cohort. Outcomes after discharge such as re-admissions, recurrent myocardial infarction and quality of life were not obtained.

**Conclusion**

Female sex was independently associated with 5.6 times higher 30-day mortality and 2.5 times higher medium-term mortality after CABG. Women have had more risk factors and comorbidities that put them at higher risk. Further research is required to identify reasons behind this and to formulate strategies to help reduce this disparity.
Competing interests: Nil.

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