ORIGINAL RESEARCH

Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based Cohort Study

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Background**—**Little attention has been paid to the importance of sex in the long-term prognosis of patients undergoing cardiac surgery.

Methods and Results**—**We conducted a retrospective cohort study of Ontario residents, aged ≥40 years, who underwent coronary artery bypass grafting (CABG) and/or aortic, mitral, or tricuspid valve surgery between October 1, 2008, and December 31, 2016. The primary outcome was all-cause mortality. The mortality rate in each surgical group was calculated using the Kaplan-Meier method. The risk of death was assessed using multivariable Cox proportional hazard models. Sex-specific mortality risk factors were identified using multiplicative interaction terms. A total of 72 824 patients were included in the study (25% women). The median follow-up period was 5 (interquartile range, 3–7) years. The long-term age-standardized mortality rate was lowest in patients who underwent isolated CABG and highest among those who underwent combined CABG/multiple valve surgery. Women had significantly higher age-standardized mortality rate than men after CABG and combined CABG/mitral valve surgery. Men had lower rates of long-term mortality than women after isolated mitral valve repair, whereas women had lower rates of long-term mortality than men after isolated mitral valve replacement. We observed a statistically significant association between female sex and long-term mortality after adjustment for key risk factors.

Conclusions**—**Female sex was associated with long-term mortality after cardiac surgery. Perioperative optimization and long-term follow-up should be tailored to younger women with a history of myocardial infarction and percutaneous coronary intervention and older men with a history of chronic obstructive pulmonary disease and depression. **(*J Am Heart Assoc*. 2019;8:e013260. DOI: 10.1161/JAHA.119.013260.)**

Key Words: cardiac surgery • coronary revascularization • mortality • sex differences • valve repair • valve replacement

Globally, 2 million cardiac surgery procedures are being performed each year.[1] Steady improvements in postoperative survival can be largely attributed to important advancements in surgical technique, perioperative risk stratification, and care.[2–4] Despite the well-established role of patient sex on disease presentation, comorbid conditions, and the development of postoperative complications,[5–7] little attention has been paid to the importance of sex in the prognosis of patients undergoing cardiac surgery.[6,8] To date, most reports of sex differences in cardiac surgery outcomes have been focused on short-term survival.[9–14] Existing sex-stratified analyses of long-term outcomes are dated, single center in nature, and/or limited to isolated coronary artery bypass grafting (CABG) or a single type of procedure.[15–18] A current and comprehensive understanding of sex-specific long-term prognosis is needed to better inform operative decisions and provide tailored follow-up strategies in cardiac surgery patients.[3,19] We, therefore, examined the sex differences in long-term survival of all patients who underwent CABG, valve, or combined CABG/valve procedures in Ontario, Canada, between 2008 and 2016.

Methods

A flow chart detailing the process used to select the study cohort is shown in Figure 1.

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Accompanying Table S1 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013260

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Clinical Perspective

What Is New?

- We systematically described the sex differences in long-term mortality after major cardiac surgery in a large, real-world cohort.
- We observed a statistically significant association between female sex and long-term mortality after adjustment for key risk factors.
- Women experienced higher rates of mortality than men after coronary artery bypass grafting and combined coronary artery bypass grafting/mitral valve surgery, and mortality risk factors differed by sex.

What Are the Clinical Implications?

- Perioperative optimization and long-term follow-up should be tailored to women with a history of recent myocardial infarction and diabetes mellitus and men with a history of chronic obstructive pulmonary disease and depression.
- Given the substantial sex differences in patient presentation for coronary and valvular heart disease, further efforts need to be directed at the education of both physicians and patients in the early recognition of acute presentation of cardiac disease in women.
- Given the poorer performance of standard risk scores in women, further research is needed to derive and validate sex-specific risk prediction models in patients undergoing cardiac surgery.

Design and Study Population

We conducted a population-based, retrospective cohort study in Ontario, Canada. The Research Ethics Board of Sunnybrook Health Sciences Centre (Toronto, Canada) approved this study and waived the need for individual patient consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Included were adult Ontario residents, aged ≥40 years, who underwent CABG and/or aortic, mitral, or tricuspid valve surgery between October 1, 2008, and December 31, 2016. For those patients who underwent multiple cardiac procedures during the study period, the first procedure was considered the index procedure. Exclusion criteria were non-Ontario residents, those with missing information on age and sex, and those who had concomitant arrhythmia, pulmonic valve, or thoracic aorta surgery. Ontario is Canada's most populous province, with a publicly funded, universal healthcare system that reimburses all covered services and providers.

Data Sources

We used the clinical registry data from CorHealth Ontario (https://www.corhealthontario.ca) and population-level administrative healthcare databases with information on all Ontario residents, available at the Institute for Clinical Evaluative Sciences. Individuals who underwent specified cardiac procedures were identified from the CorHealth Ontario registry. CorHealth Ontario maintains a detailed prospective registry of all patients who undergo invasive cardiac procedures in Ontario. All 20 advanced cardiac hospitals in Ontario participate in the registry. It captures demographic, comorbidity, and procedural-related information and has been validated through selected chart audits. In addition, CorHealth Ontario ejection fraction (EF) and angiographic data undergo core laboratory validation.[20]

Administrative databases were linked deterministically by using encrypted unique confidential codes that preserve patient confidentiality. We linked the CorHealth Ontario registry (date and type of cardiac procedures, physiologic and comorbidity data) with the Canadian Institute for Health Information's Discharge Abstract Database (comorbidities and hospital admissions) and Same Day Surgery database (comorbidities), Ontario Health Insurance Plan database (physician service claims), Registered Persons Database (ascertainment of vital statistics), and Canadian census. These administrative databases have been validated for many outcomes, exposures, and comorbidities, including heart failure (HF), chronic obstructive pulmonary disease (COPD), asthma, hypertension, myocardial infarction (MI), and diabetes mellitus.[21–24]

Comorbidities

Comorbidities were identified from the CorHealth Ontario registry and supplemented with data from the Discharge Abstract Database, Same Day Surgery database, and Ontario Health Insurance Plan database using *International Classification of Diseases, Tenth Revision* (*ICD-10-CA*), codes[25] within 5 years before the index procedure, according to validated algorithms.[21,23,26,27] We estimated socioeconomic status based on patients' neighborhood median income in the Canadian census and determined their residence (rural versus urban) using the definitions from Statistics Canada.[28] Procedural urgency was ascertained from the CorHealth Ontario registry. Height, weight, and body mass index were identified from the CorHealth Ontario registry; and they were used to define morbid obesity (weight >159 kg or body mass index ≥40 kg/m^2).[6,7,29] Frailty status was identified using the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator, which is an instrument designed and validated for research of frailty-related outcomes and resource use using administrative data.[29–34]

Outcomes

The primary outcome was all-cause mortality. We confirmed in-hospital mortality using the Discharge Abstract Database

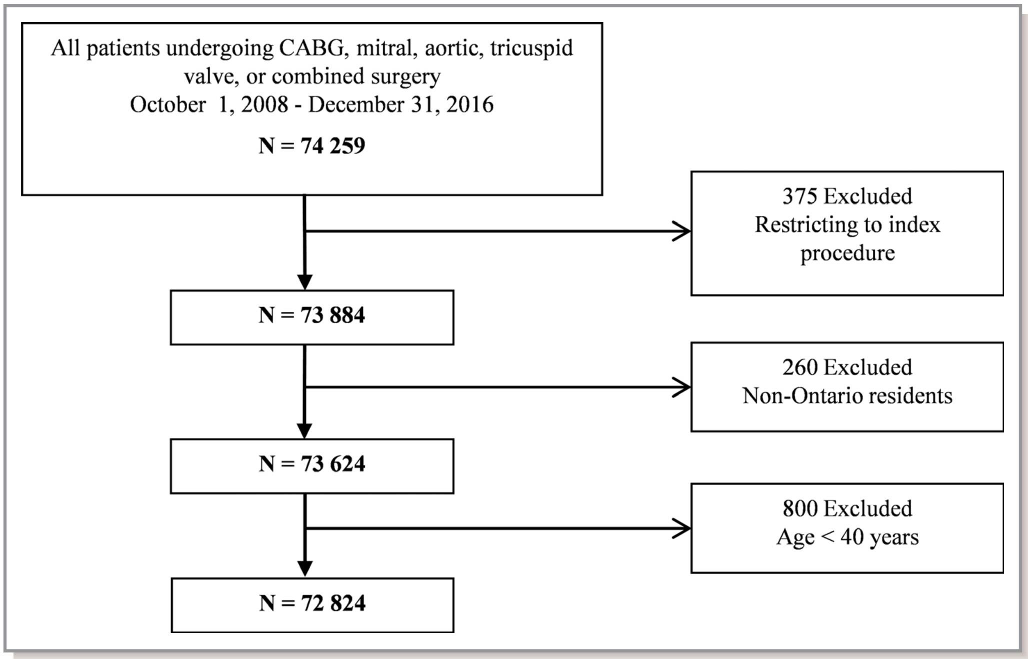

Figure 1. Cohort selection flow chart. CABG indicates coronary artery bypass grafting.

and postdischarge mortality using the Registered Persons Database.

Statistical Analysis

A.B.E. and L.Y.S. had full access to all the data in the study and take responsibility for their integrity and for the data analysis. All analyses were performed in the overall cohort and then stratified by sex. Continuous variables are expressed as mean (SD), and categorical variables are expressed as number (proportion). Outcomes were assessed through December 31, 2017. Patients were censored at the front end if they lost possession of a valid Ontario health insurance card for 2 consecutive eligibility quarters (ie, assumed to have left the province of Ontario). Event time was defined as the date of index surgery until the date of the event or the date of the last follow-up, whichever occurred earlier. Mortality rates in each group were calculated by using the Kaplan-Meier method, and differences in mortality between groups were assessed with the log-rank test. The proportionality assumption was tested by using log-log plots for sex and type of surgery. Sex-specific mortality rates were standardized by age, using the 2012 Canadian population as the reference.

The risk of death was assessed using a multivariable Cox proportional hazard model with adjustment for all variables listed in Table 1. We explored the modifying effect of sex by using multiplicative interaction terms. For the covariates that had a significant interaction effect with sex, we reported sex-stratified hazard ratios (HRs) for the covariate, as well as HRs for female sex, stratified by the presence or absence of that covariate.

As women and men differed in baseline and operative characteristics, we conducted a sensitivity analysis by using inverse probability of treatment weighting using propensity scores to estimate the effect of sex. Specifically, we used logistic regression to estimate propensity scores of being women, using the same set of covariates as those used in the multivariable Cox proportional hazards model. We used a weighted Cox proportional hazards model to estimate the effect of sex on mortality in the sample weighted by inverse probability of treatment weighting. We then used a robust sandwich variance estimator to account for the within-subject correlation in outcomes induced by weighting.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), with statistical significance defined by a 2-sided $P<0.05$.

Results

A total of 72 824 patients were included in the study (24% women). The baseline patient characteristics are summarized in Table 1. Compared with men, women were older, were more frail, had lower socioeconomic status, and were more likely to have preserved left ventricular EF and comorbid conditions, such as valvular heart disease, atrial fibrillation, hypertension, cerebrovascular and peripheral arterial disease, COPD, diabetes mellitus, hypothyroidism, and anemia. In contrast, women were less likely than men to have had an MI, to have had a previous percutaneous coronary intervention

Table 1. Baseline Characteristics, Stratified by Sex

Variable	Overall Population	No. (%) of Patients*		*P* Value
		Women (N=17 874)	Men (N=54 950)	
Surgery type				
Isolated CABG	52 546 (72.2)	10 743 (60.1)	41 803 (76.1)	<0.001
CABG+single valve†	7936 (10.9)	2098 (11.7)	5838 (10.6)	
CABG+multiple valve†	665 (0.9)	202 (1.1)	463 (0.8)	
Single valve†	10 368 (14.2)	4212 (23.6)	6156 (11.2)	
Multiple valve†	1309 (1.8)	619 (3.5)	690 (1.3)	
Age, mean±SD, y	67.0±10.2	69.1±10.1	66.2±10.1	<0.001
40–64	28 941 (39.7)	5601 (31.3)	23 340 (42.5)	<0.001
65–74	25 229 (34.6)	6206 (34.7)	19 023 (34.6)	
75–84	16 806 (23.1)	5363 (30.0)	11 443 (20.8)	
≥85	1848 (2.5)	704 (3.9)	1144 (2.1)	
Rural residence	11 763 (16.2)	2805 (15.7)	8958 (16.3)	
Income quintile				
1 (Lowest)	13 448 (18.5)	3831 (21.4)	9617 (17.5)	<0.001
2	14 696 (20.2)	3762 (21.0)	10 934 (19.9)	
3	14 759 (20.3)	3559 (19.9)	11 200 (20.4)	
4	15 017 (20.6)	3478 (19.5)	11 539 (21.0)	
5 (Highest)	14 532 (20.0)	3145 (17.6)	11 387 (20.7)	
Missing	372 (0.5)	99 (0.6)	273 (0.5)	
Hypertension	62 852 (86.3)	15 892 (88.9)	46 960 (85.5)	<0.001
Atrial fibrillation	5165 (7.1)	1621 (9.1)	3544 (6.4)	<0.001
Recent MI	22 952 (31.5)	5283 (29.6)	17 669 (32.2)	<0.001
Remote MI	11 605 (15.9)	2555 (14.3)	9050 (16.5)	<0.001
Previous PCI	10 532 (14.5)	2245 (12.6)	8287 (15.1)	<0.001
Heart failure	19 847 (27.3)	6378 (35.7)	13 469 (24.5)	<0.001
LVEF, %				
≥50	48 185 (66.2)	13 081 (73.2)	35 104 (63.9)	<0.001
35–50	15 448 (21.2)	3010 (16.8)	12 438 (22.6)	
20–35	6044 (8.3)	1123 (6.3)	4921 (9.0)	
<20	1113 (1.5)	165 (0.9)	948 (1.7)	
Missing	2034 (2.8)	495 (2.8)	1539 (2.8)	
Cerebrovascular disease	7420 (10.2)	2012 (11.3)	5408 (9.8)	<0.001
Peripheral arterial disease	9139 (12.5)	2314 (12.9)	6825 (12.4)	0.065
COPD or asthma	21 419 (29.4)	6232 (34.9)	15 187 (27.6)	<0.001
Diabetes mellitus	32 812 (45.1)	8458 (47.3)	24 354 (44.3)	<0.001
Morbid obesity	28 391 (39.0)	5449 (30.5)	22 942 (41.8)	<0.001
Hypothyroidism	1419 (1.9)	786 (4.4)	633 (1.2)	<0.001
Liver disease	633 (0.9)	161 (0.9)	472 (0.9)	0.60
Anemia	7347 (10.1)	2564 (14.3)	4783 (8.7)	<0.001
Venous thromboembolism	288 (0.4)	73 (0.4)	215 (0.4)	0.99

Continued

Table 1. Continued

Variable	Overall Population	No. (%) of Patients*		P Value
		Women (N=17 874)	Men (N=54 950)	
Dialysis	1531 (2.1)	390 (2.2)	1141 (2.1)	0.39
Baseline creatinine, μmol/L				
120–179	6635 (9.1)	1219 (6.8)	5416 (9.9)	<0.001
<120	60 190 (82.7)	15 258 (85.4)	44 932 (81.8)	
≥180	2435 (3.3)	537 (3.0)	1898 (3.5)	
Missing	3564 (4.9)	860 (4.8)	2704 (4.9)	
Chronic renal disease	3133 (4.3)	771 (4.3)	2362 (4.3)	0.93
Dementia	176 (0.2)	55 (0.3)	121 (0.2)	0.038
Depression	1089 (1.5)	417 (2.3)	672 (1.2)	<0.001
Psychosis	161 (0.2)	58 (0.3)	103 (0.2)	0.001
Primary tumor	3770 (5.2)	817 (4.6)	2953 (5.4)	<0.001
Metastatic cancer	375 (0.5)	114 (0.6)	261 (0.5)	0.008
Charlson score, median (IQR)	1 (0–3)	2 (0–3)	1 (0–3)	<0.001
Frailty‡	11 685 (16.0)	3601 (20.1)	8084 (14.7)	<0.001

CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Unless otherwise stated.
†Mitral, aortic, or tricuspid surgery.
‡According to the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator.[29–34]

(PCI), to undergo isolated CABG, to be morbidly obese, or to abuse alcohol.

Figure 2 demonstrates the relative frequencies of surgical procedures performed in women and men. Isolated CABG was the most common cardiac procedure, accounting for 72.2% of the provincial procedural volume. Although valvular procedures were performed in near equal frequencies in both sexes, most CABG and combined CABG/valve procedures were performed in men. Table 2 summarizes baseline patient characteristics according to surgery type. Isolated CABG was most likely to be

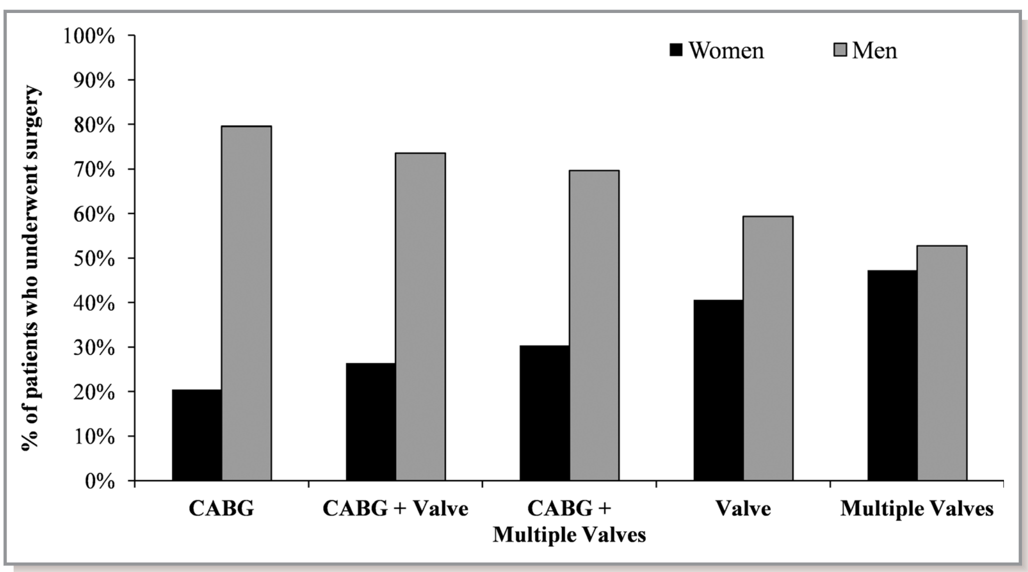

Figure 2. Percentage of men and women who underwent each of the 5 cardiac procedure categories. CABG indicates coronary artery bypass grafting.

Table 2. Baseline Characteristics, Stratified by Type of Surgery

Variable	Overall Population (N=72 824)	No. (%) of Patients* Isolated CABG (N=52 546)	CABG+Single Valve (N=7936)†	CABG+Multiple Valves (N=665)†	Single Valve (N=10 368)†	Multiple Valves (N=1309)†	*P* Value
Age, mean±SD, y	67.0±10.2	65.9±9.8	72.6±9.0	72.5±9.1	67.5±11.2	68.3±11.4	<0.001
40–64	28 941 (39.7)	22 925 (43.6)	1460 (18.4)	129 (19.4)	3969 (38.3)	458 (35.0)	<0.001
65–74	25 229 (34.6)	18 626 (35.4)	2795 (35.2)	216 (32.5)	3197 (30.8)	395 (30.2)	
75–84	16 806 (23.1)	10 220 (19.4)	3128 (39.4)	269 (40.5)	2801 (27.0)	388 (29.6)	
≥85	1848 (2.5)	775 (1.5)	553 (7.0)	51 (7.7)	401 (3.9)	68 (5.2)	
Rural residence	11 763 (16.2)	8204 (15.6)	1457 (18.4)	143 (21.5)	1756 (16.9)	203 (15.5)	
Income quintile							
1 (Lowest)	13 448 (18.5)	10 003 (19.0)	1370 (17.3)	102 (15.3)	1728 (16.7)	245 (18.7)	<0.001
2	14 696 (20.2)	10 724 (20.4)	1608 (20.3)	148 (22.3)	1959 (18.9)	257 (19.6)	
3	14 759 (20.3)	10 627 (20.2)	1609 (20.3)	157 (23.6)	2117 (20.4)	249 (19.0)	
4	15 017 (20.6)	10 714 (20.4)	1705 (21.5)	127 (19.1)	2214 (21.4)	257 (19.6)	
5 (Highest)	14 532 (20.0)	10 184 (19.4)	1617 (20.4)	129 (19.4)	2310 (22.3)	292 (22.3)	
Missing	372 (0.5)	294 (0.6)	27 (0.3)	≤5	40 (0.4)	9 (0.7)	
Hypertension	62 852 (86.3)	46 111 (87.8)	7185 (90.5)	595 (89.5)	7954 (76.7)	1007 (76.9)	<0.001
Atrial fibrillation	5165 (7.1)	2373 (4.5)	990 (12.5)	155 (23.3)	1343 (13.0)	304 (23.2)	<0.001
Recent MI	22 952 (31.5)	20 684 (39.4)	1659 (20.9)	132 (19.8)	422 (4.1)	55 (4.2)	<0.001
Remote MI	11 605 (15.9)	9432 (17.9)	1295 (16.3)	108 (16.2)	679 (6.5)	91 (7.0)	<0.001
Previous PCI	10 532 (14.5)	8773 (16.7)	1004 (12.7)	68 (10.2)	617 (6.0)	70 (5.3)	<0.001
Heart failure	19 847 (27.3)	10 126 (19.3)	3714 (46.8)	430 (64.7)	4729 (45.6)	848 (64.8)	<0.001
LVEF, %							
≥50	48 185 (66.2)	32 237 (61.4)	5630 (70.9)	435 (65.4)	8843 (85.3)	1040 (79.4)	
35–50	15 448 (21.2)	12 762 (24.3)	1398 (17.6)	145 (21.8)	967 (9.3)	176 (13.4)	
20–35	6044 (8.3)	4911 (9.3)	654 (8.2)	66 (9.9)	346 (3.3)	67 (5.1)	
<20	1113 (1.5)	905 (1.7)	139 (1.8)	13 (2.0)	43 (0.4)	13 (1.0)	
Missing	2034 (2.8)	1731 (3.3)	115 (1.4)	6 (0.9)	169 (1.6)	13 (1.0)	<0.001
Cerebrovascular disease	7420 (10.2)	5132 (9.8)	1073 (13.5)	82 (12.3)	970 (9.4)	163 (12.5)	<0.001
Peripheral arterial disease	9139 (12.5)	6424 (12.2)	1389 (17.5)	108 (16.2)	1079 (10.4)	139 (10.6)	<0.001
COPD or asthma	21 419 (29.4)	14 702 (28.0)	2726 (34.3)	251 (37.7)	3301 (31.8)	439 (33.5)	<0.001
Diabetes mellitus	32 812 (45.1)	25 267 (48.1)	3639 (45.9)	266 (40.0)	3218 (31.0)	422 (32.2)	<0.001
Morbid obesity	28 391 (39.0)	20 490 (39.0)	3106 (39.1)	281 (42.3)	3951 (38.1)	563 (43.0)	0.004
Hypothyroidism	1419 (1.9)	969 (1.8)	186 (2.3)	18 (2.7)	206 (2.0)	40 (3.1)	<0.001
Liver disease	633 (0.9)	351 (0.7)	81 (1.0)	11 (1.7)	153 (1.5)	37 (2.8)	<0.001
Anemia	7347 (10.1)	4918 (9.4)	1113 (14.0)	136 (20.5)	977 (9.4)	203 (15.5)	<0.001
Venous thromboembolism	288 (0.4)	173 (0.3)	46 (0.6)	≤5	57 (0.5)	10 (0.8)	<0.001
Dialysis	1531 (2.1)	1047 (2.0)	233 (2.9)	22 (3.3)	195 (1.9)	34 (2.6)	<0.001
Baseline creatinine, μmol/L							
120–179	6635 (9.1)	4487 (8.5)	1037 (13.1)	93 (14.0)	855 (8.2)	163 (12.5)	<0.001
<120	60 190 (82.7)	43 934 (83.6)	6158 (77.6)	522 (78.5)	8538 (82.3)	1038 (79.3)	
≥180	2435 (3.3)	1698 (3.2)	381 (4.8)	32 (4.8)	261 (2.5)	63 (4.8)	
Missing	3564 (4.9)	2427 (4.6)	360 (4.5)	18 (2.7)	714 (6.9)	45 (3.4)	

Continued

Table 2. Continued

Variable	Overall Population (N=72 824)	No. (%) of Patients* Isolated CABG (N=52 546)	CABG+Single Valve (N=7936)†	CABG+Multiple Valves (N=665)†	Single Valve (N=10 368)†	Multiple Valves (N=1309)†	*P* Value
Chronic renal disease	3133 (4.3)	2109 (4.0)	516 (6.5)	43 (6.5)	399 (3.8)	66 (5.0)	<0.001
Dementia	176 (0.2)	98 (0.2)	41 (0.5)	6 (0.9)	27 (0.3)	≤5	<0.001
Depression	1089 (1.5)	733 (1.4)	149 (1.9)	13 (2.0)	157 (1.5)	37 (2.8)	<0.001
Psychosis	161 (0.2)	102 (0.2)	17 (0.2)	≤5	33 (0.3)	6 (0.5)	0.025
Primary tumor	3770 (5.2)	2486 (4.7)	539 (6.8)	48 (7.2)	601 (5.8)	96 (7.3)	<0.001
Metastatic cancer	375 (0.5)	248 (0.5)	40 (0.5)	≤5	72 (0.7)	10 (0.8)	0.03
Charlson score, median (IQR)	1 (0–3)	2 (0–3)	2 (0–3)	2 (1–3)	1 (0–2)	1 (0–2)	<0.001
Frailty‡	11 685 (16.0)	8623 (16.4)	1491 (18.8)	154 (23.2)	1204 (11.6)	213 (16.3)	<0.001

CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Unless otherwise stated.
†Mitral, aortic, or tricuspid valve surgery.
‡According to the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator.[29–34]

performed in younger men with a history of reduced left ventricular EF and previous MI and PCI; but least likely to be performed in those with HF. Compared with those who underwent combined CABG/valve procedures, those who underwent isolated valve surgery were younger and were more likely to have preserved left ventricular EF and a lower burden of comorbidities, as evidenced by a lower Charlson comorbidity index. Those who underwent combined CABG/multiple valve surgery were among the frailest and burdened with the highest number of comorbidities. The proportionality assumption was satisfied for age and type of surgery.

Survival at 30 Days

Overall, women were more likely to die than men during the first 30 days after surgery (2.7% versus 1.6%; $P<0.001$). Thirty-day mortality rates after isolated CABG, CABG/single-valve, CABG/multiple-valve, single-valve, and multiple-valve surgery were 1.4%, 4.0%, 7.5%, 1.7%, and 5.2%, respectively ($P<0.001$). The sex- and procedure-stratified 30-day crude and age-standardized mortality rates (AMRs) are summarized in Table 3.

Sex Differences in Long-Term Survival

The median follow-up period was 5 years (interquartile range, 3–7 years), and the maximum follow-up period was 9 years. Women were more likely than men to die within 1 year after a cardiac procedure (6.2% versus 4.1%; $P<0.001$) and during long-term follow-up (19.0% versus 14.8%; $P<0.001$). The multivariable adjusted long-term survival curves for women and men are illustrated in Figure 3.

Sex modified the correlation between mortality and type of surgery, age, recent and remote MI, previous PCI, COPD/asthma, and depression. The HRs for sex, stratified by the presence or absence of these characteristics, are presented in Table 4; the sex-stratified HRs for the same characteristics are presented in Table 5. Taken together, women who underwent surgery involving CABG had a higher risk of death than men (Table 4); and this observation was especially evident in women who underwent CABG/multiple valve reconstruction (Table 5). Although female sex accentuated the risk of long-term mortality in patients aged <75 years (Table 4), the association between sex and long-term mortality was more accentuated in men aged >75 years compared with women of the same age group (Table 5). In addition, although remote MI, recent MI, and previous PCI were associated with higher risks of death in women (Table 4), previous PCI was associated with a lower risk of death in men and not in women (Table 5). Both COPD/asthma and depression were associated with a slightly higher risk of death in men compared with women (Table 5).

In the sensitivity analysis in which we used inverse probability of treatment weighting of the propensity score, we found female sex to be associated with a higher risk of death (HR, 1.10; 95% CI, 1.05–1.16).

Long-Term Survival by Surgery Type

The sex- and procedure-specific mortality rates are shown in Table 5. Overall, long-term AMRs were lowest in patients who underwent isolated CABG, followed by single-valve, multiple-valve, CABG/single-valve, and CABG/multiple-valve surgeries. AMRs after isolated CABG and combined CABG/single-valve

Table 3. CMRs and AMRs Within 30 Days and in Long-Term Follow-Up After Surgery

Surgery	Sex	No. of Deaths	Person-Years	CMR per 1000 Person-Years (95% CI)	AMR per 1000 Person-Years (95% CI)	*P* Value
30-d Mortality						
CABG	Women	235	317 222	0.7 (0.7–0.8)	0.6 (0.5–0.7)	<0.001
	Men	506	1 244 223	0.4 (0.4–0.4)	0.4 (0.3–0.4)	
CABG+single valve*	Women	112	60 505	1.9 (1.5–2.2)	1.6 (1.1–2.4)	0.008
	Men	207	171 205	1.2 (1.1–1.4)	0.9 (0.7–1.2)	
CABG+multiple valve*	Women	22	5588	3.9 (2.5–6.0)	2.0 (0.9–3.9)	0.95
	Men	28	13 298	2.1 (1.4–3.0)	2.0 (0.9–3.7)	
Single valve*	Women	87	124 712	0.7 (0.6–0.9)	0.6 (0.4–0.7)	0.11
	Men	90	183 088	0.5 (0.4–0.6)	0.4 (0.3–0.5)	
Multiple valve*	Women	30	17 971	1.7 (1.13–2.38)	1.2 (0.7–2.0)	0.17
	Men	38	19 951	1.9 (1.35–2.61)	1.9 (1.2–2.7)	
Long-term mortality						
CABG	Women	1749	49 723	35.2 (33.6–36.9)	28.4 (26.7–30.1)	<0.001
	Men	5219	196 646	26.5 (25.8–27.3)	23.6 (22.8–24.5)	
CABG+single valve*	Women	647	8869	73.0 (67.4–78.8)	58.2 (49.7–67.6)	0.01
	Men	1567	24 420	64.2 (61.0–67.4)	46.5 (42.9–50.3)	
CABG+multiple valve*	Women	79	687	115.0 (91.1–143.4)	75.2 (51.4–106.2)	0.59
	Men	149	1758	84.8 (71.7–99.5)	66.6 (49.5–87.7)	
Single valve	Women	802	18 803	42.7 (39.8–45.7)	29.7 (27.0–32.6)	0.64
	Men	1055	27 352	38.6 (36.3–41.0)	30.5 (28.4–32.7)	
Multiple valve	Women	126	2253	55.9 (46.6–66.6)	41.7 (32.0–53.3)	0.11
	Men	165	2685	61.5 (52.4–71.6)	53.7 (44.3–64.4)	

AMR indicates age-standardized mortality rate; CABG, coronary artery bypass grafting; CMR, crude mortality rate.
*Mitral, aortic, or tricuspid valve surgery.

procedures were significantly higher in women than men. After CABG/multiple-valve surgeries, women had numerically higher AMR than men, whereas after multiple-valve surgery, men had numerically higher AMR than women. There were no sex-based differences in long-term survival after single-valve surgery. The adjusted Kaplan-Meier survival curves (Figure 4) also support these findings.

As long-term survival differed by surgery type, we also determined the valve-specific mortality rates and HRs for the most commonly performed surgical procedures (ie, aortic valve, mitral valve, CABG/aortic valve, CABG/mitral valve, and combined mitral/aortic valve) (Figure S1). We found that women had higher AMRs compared with men after isolated CABG ($P<0.001$) and combined CABG/mitral valve procedures ($P=0.005$). There were no statistically significant differences in long-term survival between sexes after procedures other than isolated CABG and combined CABG/mitral valve surgery.

We then examined those who had isolated mitral or aortic valve procedures for any sex-specific differences in outcomes. Specifically, we compared the long-term mortality of women versus men, who underwent the following: (1) mitral valve repair versus replacement (Figure 5) and (2) simple (ie, isolated) aortic valve replacement (AVR) versus complex AVR (ie, involving root reconstruction and/or coronary reimplantation) (Figure 6). In patients who underwent isolated mitral valve surgery, those who underwent repair had higher rates of long-term survival compared with those who had replacement surgery. In addition, in patients who had mitral valve repair, men had higher rates of long-term survival than women. Conversely, in those who had mitral valve replacement (MVR), women had higher rates of long-term survival than men. In patients who underwent isolated AVR, there were no statistically significant differences in long-term survival when comparing simple with complex procedure and women with men.

We conducted a post hoc analysis to determine whether there were sex differences in the type of surgery performed during an acute, nonelective cardiac admission (Table S1). We found that women were more likely than men to have isolated

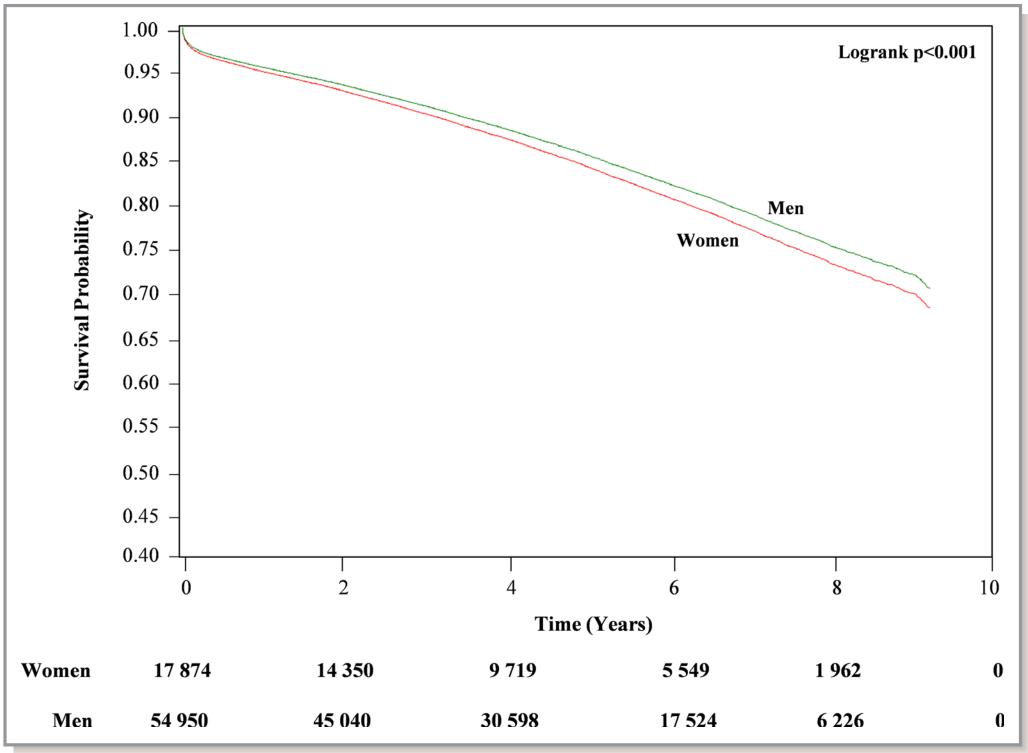

Figure 3. Adjusted Kaplan-Meier curves of long-term survival in women and men.

CABG during an acute cardiac admission. There were no sex differences in other urgent procedures performed.

Discussion

In this population-based study, we found patient sex to be an important determinant of long-term survival after cardiac surgery. Three main findings were derived from this study. (1) Long-term AMR was lowest in patients who underwent isolated CABG and highest among those who underwent combined CABG/multiple valve surgery. (2) Women had significantly higher AMRs than men after CABG and combined CABG/mitral valve surgery. Overall, AMR was numerically higher in women than men after any procedure involving coronary revascularization. (3) Men had higher rates of long-term survival than women after isolated mitral valve repair, whereas women had higher rates of long-term survival than men after isolated MVR.

Sex Differences in Long-Term Survival After Cardiac Surgery

It is well documented that compared with men, women who present for CABG are older, have a smaller body surface area, are more likely to require an urgent/emergent operation, and have a greater burden of comorbid conditions, such as diabetes mellitus, hypertension, HF, cerebrovascular disease, and anemia.[6,11,12,35–37] Similar sex differences in comorbidities have been noted in patients presenting for isolated mitral,[17,38,39] aortic valve,[15] and concomitant CABG and valve surgeries.[40] Our results corroborate these findings in that women presenting for cardiac surgery were older, more frail, and more medically complex than men. In addition, women with cardiovascular diseases often experience a delay in diagnosis and treatment when compared with men, which may, in part, explain the more advanced coronary or valvular pathological conditions observed in women at the time of surgery.[6,41,42] These established sex differences explain our overall observation of lower estimated long-term survival in women after cardiac surgery, and of female sex being an independent risk factor for long-term mortality.

The Impact of Procedure Type on Survival

We found that valvular procedures were performed in near equal frequencies in both sexes, whereas procedures involving coronary revascularization were performed much more frequently in men. These findings are consistent with the literature.[6,43,44] Female sex has been reported as an independent risk factor for perioperative mortality as well as mortality within 5 years of CABG.[6,7,35,45,46] However, sex does not consistently influence survival after 5 years.[9,14,40,47,48] Nicolini et al,[48] in a study of 1332 women and 5976 men who underwent isolated CABG in Italy between 2003 and 2013,

Table 4. Impact of Female Sex, Stratified by the Presence and Absence of Characteristics That Have a Significant Interaction Effect With Sex

Characteristics	Adjusted HR for Women (95% CI)		Interaction *P* Value
	Presence of Characteristic	Absence of Characteristic	
Surgery			
CABG	1.15 (1.08–1.21)	. . .	0.03
CABG+single valve*	1.11 (1.01–1.22)	. . .	
CABG+multiple valves*	1.34 (1.02–1.77)	. . .	
Single valve*	1.06 (0.96–1.16)	. . .	
Multiple valves*	0.82 (0.65–1.04)	. . .	
Age group, y			
40–64	1.22 (1.11–1.34)	. . .	0.001
65–74	1.20 (1.11–1.29)	. . .	
75–84	1.04 (0.97–1.10)	. . .	
≥85	0.97 (0.84–1.13)	. . .	
Recent MI	1.27 (1.19–1.36)	1.03 (0.98–1.09)	<0.001
Remote MI	1.21 (1.11–1.32)	1.09 (1.04–1.14)	0.03
Previous PCI	1.24 (1.11–1.39)	1.10 (1.05–1.15)	0.04
COPD/asthma	1.06 (1.00–1.13)	1.16 (1.09–1.22)	0.05
Depression	0.88 (0.71–1.11)	1.12 (1.07–1.17)	0.04

CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Mitral, aortic, or tricuspid valve surgery.

found no sex difference in survival at mean follow-up of 8 years. In a study of 607 women and 3326 men who underwent isolated CABG in Stockholm, Sweden, between 1980 and 1989, significant sex differences in survival were observed at 30 days but not in long-term (5-year) follow-up.[49] This study compared 5-year mortality in women and men who survived the index surgical admission, thus removing the contribution of early female mortality to the calculation of long-term risk. In addition, this study has a small sample size, especially in the female group; and temporal changes in surgical outcomes, as well as geographic differences in surgical practice and health-seeking behavior, may in part explain these differences in results. A recent meta-analysis[45] showed that female sex was an independent risk factor for mortality at 5 years after isolated CABG (random-effects odds ratio, 1.14; 95% CI (confidence interval), 1.08–1.20; I^2=0%). This observation is in keeping with the current study, in which we found the HR associated with female sex to be 1.10 (95% CI, 1.05–1.16) after inverse probability of treatment weighting using the propensity score. In addition, poorer survival after CABG in women may be attributed to smaller coronary size,[50] which may contribute to technical challenges,[12,51] the risk of graft-coronary mismatch, and incomplete revascularization.[52,53] The diagnosis of coronary artery disease may be delayed in women compared with men, possibly because of the likelihood for an atypical presentation to coronary artery disease for women.[54] Women are also older, have a higher burden of comorbidities, are more likely to have been hospitalized for HF within 90 days and 1 year before CABG,[6] and have higher rates of postoperative complications, such as new-onset dialysis and late cardiac readmission.[6,48,55,56] In addition, our post hoc analysis found that women were more likely than men to have isolated CABG during an acute cardiac admission, which may, in part, explain their poorer prognosis.

Limited knowledge has been generated to date on the long-term outcomes after combined CABG/valve surgery. We found that among those who underwent valvular surgery with concomitant CABG, women had numerically, albeit nonstatistically significantly, higher AMRs when compared with men. Sex was not a risk factor for long-term survival after combined CABG/valve surgery. Our findings corroborate a small case series of 1567 patients who had combined CABG and aortic, mitral, or multiple-valve surgeries in Toronto, Canada, between 1990 and 2000, in which women and men had similar rates of survival at 5.3 years of follow-up.[40] In a more recent cohort of 5867 patients undergoing combined CABG and aortic valve surgery (33% women), the risk of in-hospital mortality was higher in women compared with men (odds ratio, 2.00; 95% CI, 1.44–2.79). Long-term outcomes were not examined.[44] These authors concluded that substantial sex

Table 5. Sex-Specific Risk Factors of Long-Term Mortality

Characteristics	Adjusted HR (95% CI)		Interaction *P* Value
	Women	Men	
Surgery			
CABG	Reference	Reference	0.03
CABG+single valve*	1.39 (1.27–1.53)	1.43 (1.35–1.53)	
CABG+multiple valves*	1.92 (1.53–2.42)	1.64 (1.39–1.94)	
Single valve*	1.23 (1.12–1.35)	1.34 (1.24–1.44)	
Multiple valves*	1.24 (1.03–1.49)	1.73 (1.47–2.03)	
Age group, y			
40–64	Reference	Reference	0.001
65–74	1.71 (1.54–1.89)	1.74 (1.64–1.85)	
75–84	2.78 (2.52–3.07)	3.28 (3.09–3.49)	
≥85	4.24 (3.66–4.91)	5.31 (4.79–5.9)	
Recent MI	1.30 (1.21–1.40)	1.05 (1.00–1.11)	<0.001
Remote MI	1.27 (1.17–1.38)	1.14 (1.08–1.20)	0.03
Previous PCI	1.06 (0.96–1.17)	0.93 (0.87–0.99)	0.04
COPD/asthma	1.26 (1.18–1.35)	1.37 (1.31–1.43)	0.05
Depression	1.20 (1.00–1.44)	1.52 (1.32–1.75)	0.04

CABG indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Mitral, aortic, or tricuspid valve surgery.

differences existed in patient presentation and mortality risk factors, and that standard risk scores, such as the EuroSCORE, did not perform as well in women as in men.

The sex differences in long-term outcomes after combined CABG/mitral valve surgery have not been systematically reported. In the current study, we found a significantly higher AMR in women undergoing CABG/mitral valve surgery. This could be attributed to the poorer prognosis after CABG in women with HF,[6,7] as those needing combined CABG/mitral valve surgery are more likely to have HF with reduced EF. The presence of HF compounds the sex-specific challenges in patients with coronary artery disease and further places women at risk.

We found no sex differences in long-term survival after single-valve surgery. This finding was likely driven by a higher overall number of AVRs performed compared with mitral valve surgery. In a nationwide study of all patients undergoing MVR in the Netherlands between 2007 and 2011 (N=3411; 42% women), no sex differences were reported for mortality in the hospital.[43] Long-term outcomes were not evaluated in this study. In a study of 743 patients (28% women) who underwent mitral repair for degenerative mitral regurgitation between 2001 and 2014 in Ottawa, Canada,[57] sex differences in survival were not observed at 5 years. However, the authors found that women were more likely to present with more advanced disease than men at the time of surgery. A study of 183 792 Medicare beneficiaries, between 2000 and 2009, found no difference in long-term survival by sex after mitral valve surgery. However, the authors found that women were more likely to receive mitral replacement instead of repair, and that repair restored life expectancy for men but not for women.[18] In a cohort of 3118 (40.4% women) who had MVR or AVR in Ottawa, Canada, between 1976 and 2006, no statistically significant sex differences were observed in survival after MVR.[58] The same authors also found women to have a lower risk of mortality 5.6 years after bioprosthetic AVR (adjusted HR, 0.5; 95% CI, 0.3–0.6), but no difference in survival between sexes after mechanical AVR. We also found that life expectancy was higher in men than women after mitral valve repair; however, women had higher life expectancy after MVR than men. In our subgroup of patients who underwent isolated AVR, we found no sex differences in long-term survival irrespective of the complexity of surgery. The findings of the Ottawa study[58] pertaining to survival after bioprosthetic AVR differ from the current province-wide study and may reflect center-based practice and experience with selection of mechanical versus bioprosthetic valves.

Limitations

This study has several limitations. First, the sex differences in outcomes are representative of surgical practice in Ontario.

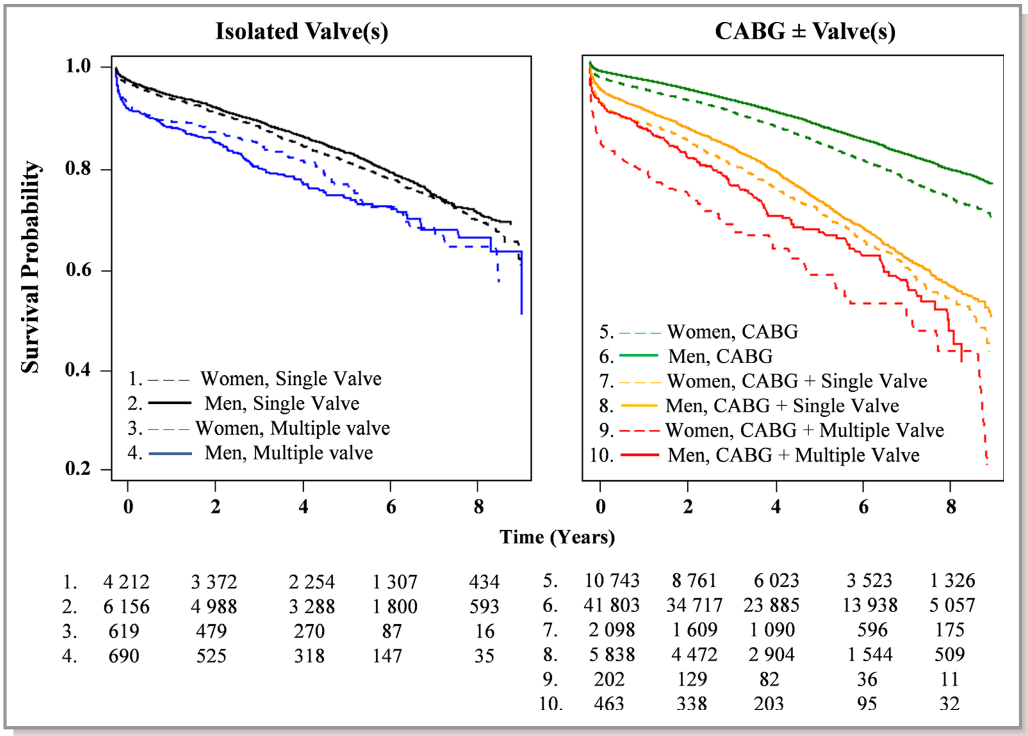

Figure 4. Adjusted survival curves in patients who underwent isolated valvular procedures (**left**) and those who underwent procedures involving coronary revascularization (**right**). CABG indicates coronary artery bypass grafting.

Similar research needs to be conducted in other settings to confirm the generalizability of our findings. Second, our data sources lacked details about the specific valve implant type (ie, bioprosthetic versus mechanical, and brand name) or repair technique. This precluded us from being able to examine sex-specific differences in outcomes in detail. Third, we lacked some details about patient characteristics, such as race and ethnicity, which some studies have shown may be independent predictors of mortality after cardiac surgery.[59] The inability to measure, and thereby adjust for, differences in

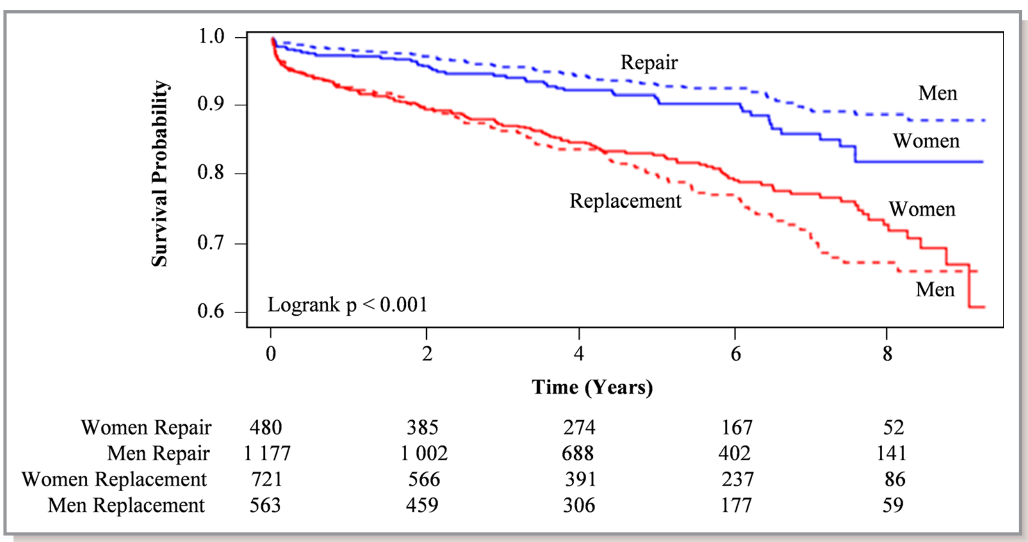

Figure 5. Kaplan-Meier survival curves in women and men who underwent mitral valve repair vs replacement.

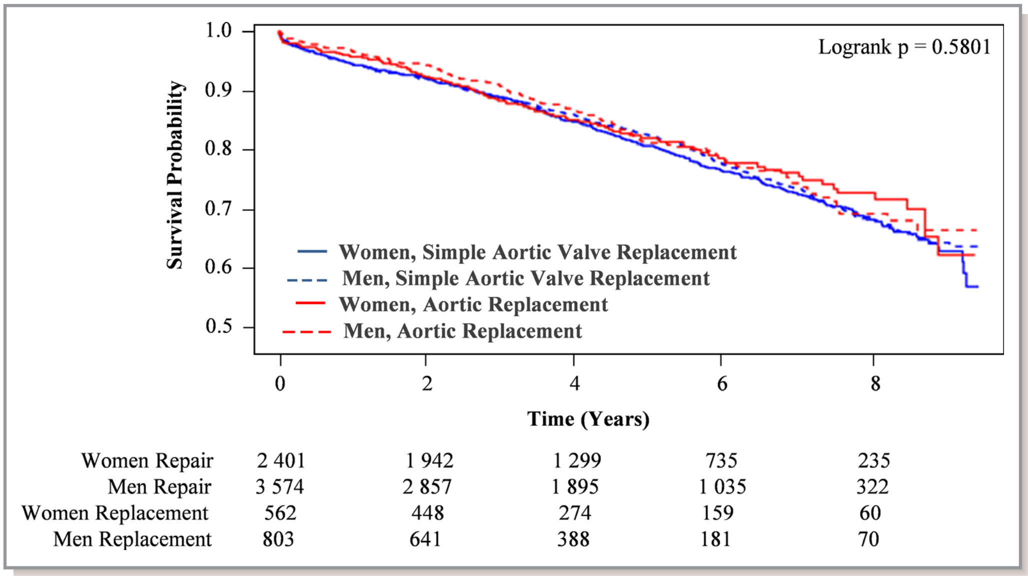

Figure 6. Kaplan-Meier survival curves of women and men who underwent simple vs complex aortic valve replacement.

such characteristics could have explained, in part, the differences in mortality observed in this study. Third, cohort studies are by nature subject to residual confounding.

Conclusions

We described the sex differences in long-term outcomes after a variety of cardiac procedures in a large, real-world cohort. We found a statistically significant association between female sex and long-term mortality after cardiac surgery. Specifically, women experienced higher rates of mortality than men after CABG and combined CABG/mitral valve surgery, and mortality risk factors also differed by sex. Perioperative optimization and long-term follow-up should be tailored to younger women with a history of MI and previous PCI and older men with a history of COPD and depression. Given the substantial sex differences in patient presentation for coronary and valvular heart disease, further efforts need to be directed at the education of both physicians and patients in the early recognition of acute presentation of cardiac disease in women. In addition, given the poorer performance of standard risk scores in women, further research is needed to derive and validate sex-specific risk prediction models in patients undergoing cardiac surgery.

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Disclosures

None.

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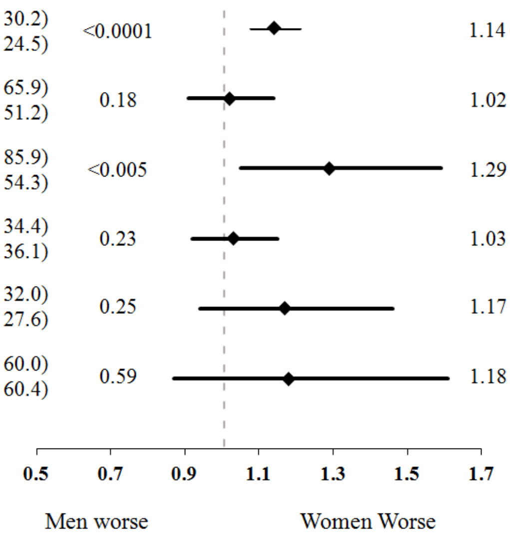
SUPPLEMENTAL MATERIAL

Table S1. Proportion of patients with surgeries performed during an acute, non-elective hospital admission, stratified by sex and procedure type.

	No. (%) of patients		
Surgery Type	**Women**	**Men**	**P-Value**
CABG	5 316 (49.5)	18 388 (44.0)	< 0.001
CABG + Single Valve	144 (6.9)	416 (7.1)	0.69
CABG + Multiple Valves	13 (6.4)	28 (6.1)	0.85
Single Valve	19 (0.5)	28 (0.5)	0.98
Multiple Valves	7 (1.1)	6 (0.9)	0.63

Figure S1. Crude and age-standardized mortality rates and adjusted hazard ratios, stratified by sex and procedure type.

Surgery	Deaths/ PY at Risk	AMR/1000 PY (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
CABG	**W:** 1 749 / 49 723 **M:** 5 219 / 196 646	**W:** 28.4 (26.7 - 30.2) **M:** 23.6 (22.8 - 24.5)	<0.0001	1.14 (1.08 – 1.21)	<0.0001
CABG + Aortic Valve	**W:** 482 / 6 884 **M:** 1 281 / 19 432	**W:** 54.0 (43.7 - 65.9) **M:** 46.4 (42.0 - 51.2)	0.18	1.02 (0.91 – 1.14)	0.73
CABG + Mitral Valve	**W:** 164 / 1 972 **M:** 281 / 4 938	**W:** 68.8 (54.3 - 85.9) **M:** 46.6 (39.7 - 54.3)	<0.005	1.29 (1.05 – 1.59)	0.017
Aortic Valve	**W:** 607 / 13 203 **M:** 846 / 19 081	**W:** 30.4 (26.8 - 34.4) **M:** 33.3 (30.6 - 36.1)	0.23	1.03 (0.92 – 1.15)	0.65
Mitral Valve	**W:** 184 / 5 511 **M:** 202 / 8 194	**W:** 27.0 (22.6 - 32.0) **M:** 23.6 (20.0 - 27.6)	0.25	1.17 (0.94 – 1.46)	0.16
Mitral + Aortic Valve	**W:** 91 / 1 576 **M:** 133 / 2 274	**W:** 44.7 (32.5 - 60.0) **M:** 49.2 (39.7 - 60.4)	0.59	1.18 (0.87 – 1.61)	0.28



CABG = coronary artery bypass surgery; AMR = age-standardized mortality rate; PY = person-years; CI = confidence interval; M= men; W= women