CJC Open 5 (2023) 220–229

Original Article

Population Study of Sex-Based Outcomes After Surgical Aortic Valve Replacement

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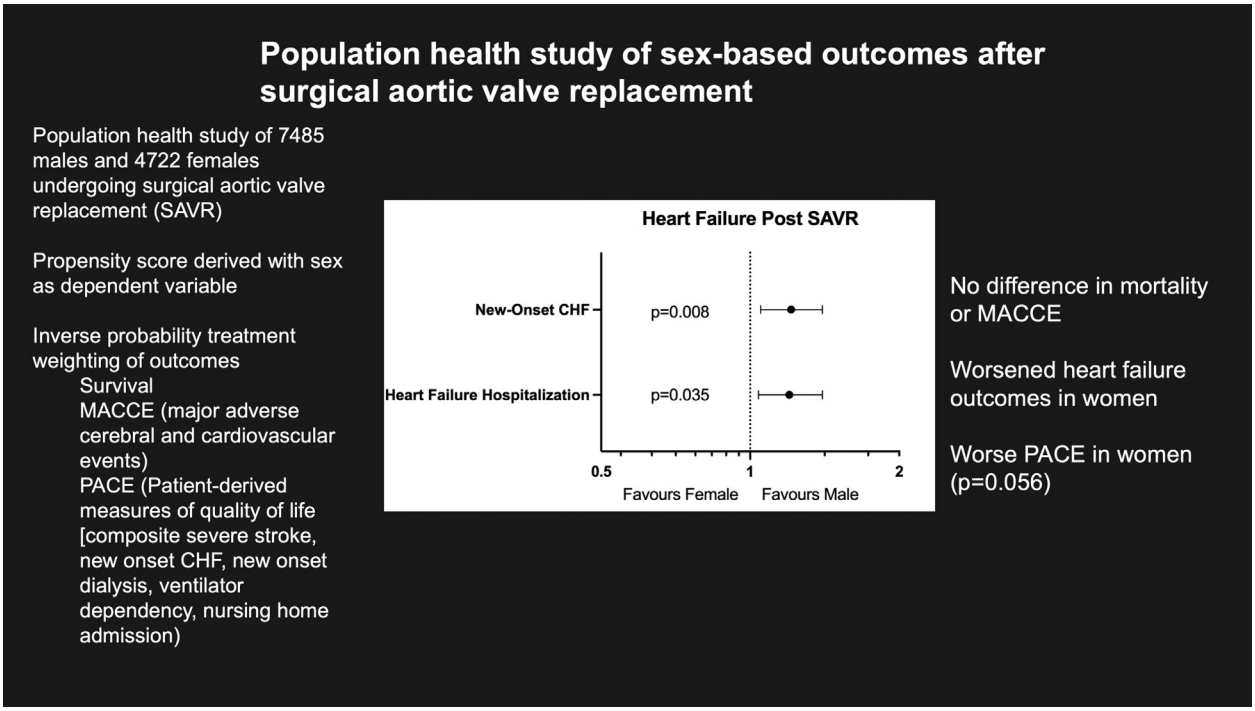

ABSTRACT

Background: Surgical aortic valve replacement (SAVR) is a key strategy for the treatment of aortic valve disease. However, studies have involved primarily male patients, and whether the benefits of this approach can be extrapolated to female patients is unclear.

Methods: Clinical and administrative datasets for 12,207 patients undergoing isolated SAVR in Ontario from 2008 to 2019 were linked. Male and female patients were balanced using inverse probability

RÉSUMÉ

Contexte : La chirurgie de remplacement valvulaire aortique est une stratégie importante dans le traitement de la valvulopathie aortique. Cependant, les études ont été menées principalement auprès de patients masculins, et il est difficile d'affirmer si les avantages de cette approche peuvent être extrapolés aux patientes.

Méthodologie : Les ensembles de données cliniques et administratives de 12 207 patients ayant subi uniquement une chirurgie de

https://doi.org/10.1016/j.cjco.2022.12.001

treatment weighting. Mortality, endocarditis, and major hemorrhagic and thrombotic events, as well as 2 composite outcomes—major adverse cerebral and cardiovascular events (MACCE) and patient-derived adverse cardiovascular and noncardiovascular events (PACE)—and their component events, were compared in the weighted groups with a stratified log-rank test.

Results: A total of 7485 male patients and 4722 female patients were included in the study. Median follow-up was 5.2 years in both sexes. All-cause mortality did not differ between sexes (hazard ratio [HR] 0.949 [95% confidence interval {CI} 0.851-1.059]). Male sex was associated with an increased risk of new-onset dialysis (HR 0.689 [95% CI 0.488-0.974]). Female sex was associated with a significantly increased risk of both new-onset heart failure (HR 1.211 [95% CI 1.051-1.394], $P = 0.0081$) and heart failure hospitalization (HR 1.200 [95% CI 1.036-1.390], $P = 0.015$). No statistically significant differences were seen in any of the other secondary outcomes between sexes.

Conclusions: This population health study demonstrated that survival did not differ between male and female patients undergoing SAVR. Significant sex-related differences were found in the risk of heart failure and new-onset dialysis, but these findings should be considered exploratory and require further study.

remplacement valvulaire aortique en Ontario entre 2008 et 2019 ont été regroupés. Les groupes de patients hommes et femmes ont été équilibrés à l'aide d'une pondération par probabilité inverse du traitement. La mortalité, l'endocardite et les événements hémorragiques et thrombotiques majeurs en plus de deux critères composés — les événements cérébrovasculaires et cardiovasculaires indésirables majeurs et les événements cardiovasculaires et non cardiovasculaires indésirables rapportés par les patients — et leurs événements constituants ont été comparés dans les groupes pondérés à l'aide d'un test logarithmique par rangs stratifié.

Résultats : Au total, 7485 hommes et 4722 femmes ont été inclus dans l'étude. La durée médiane du suivi était de 5,2 ans chez les femmes comme chez les hommes. La mortalité toutes causes confondues ne différait pas entre les sexes (rapport de risques instantanés [RRI] : 0,949, intervalle de confiance [IC] à 95 % : 0,851 à 1,059). Le sexe masculin était associé à un risque accru d'instauration d'une dialyse (RRI : 0,689; IC à 95 % : 0,488 à 0,974). Le sexe féminin était associé à une augmentation significative du risque d'insuffisance cardiaque inaugurale (RRI : 1,211; IC à 95 % : 1,051 à 1,394; $p = 0,0081$) et d'hospitalisation pour une insuffisance cardiaque (RRI : 1,200; IC à 95 % : 1,036 à 1,390; $p = 0,015$). Aucune différence statistiquement significative n'a été notée entre les sexes pour les autres critères secondaires.

Conclusions : Cette étude en santé des populations a montré que la survie chez les personnes subissant une chirurgie de remplacement valvulaire aortique ne diffère pas entre les hommes et les femmes. Des différences significatives fondées sur le sexe ont été notées dans le risque d'insuffisance cardiaque et de l'instauration d'une dialyse, mais ces constats doivent être considérés comme exploratoires et faire l'objet d'autres études.

Aortic valvular disease is a major contributor to cardiovascular morbidity worldwide. Despite growth in the use of transcatheter aortic valve implantation (TAVI), surgical aortic valve replacement (SAVR) remains a key strategy in the treatment of these patients.[1] Evidence supports the possibility of sex-related differences in outcomes after such cases of SAVR. The pathophysiology of aortic stenosis differs between the sexes, and outcomes of female patients presenting with aortic stenosis may be suboptimal due to several factors, including delayed presentation, higher comorbidity,[2,3] and a higher incidence of low-gradient stenosis.[4] Similarly, aortic insufficiency in female patients is characterized by different mechanisms of left ventricular remodelling,[5] and female patients often have a significantly greater symptom burden at the time of valve replacement.[6]

Several other studies have examined sex-based differences in medium- to long-term survival after SAVR. In a population health study from Finland, male and female participants were matched pairwise by propensity scores (PSs). No outcome differences were demonstrated. However, the PS derivation was based on only a few covariates, missing important characteristics such as diabetes and body size.[7] This trial measured survival but did not report heart failure (HF) outcomes. The **S**wedish **W**eb-System for **E**nhancement and **D**evelopment of **E**vidence-Based Care in **H**eart Disease **E**valuated **A**ccording to **R**ecommended **T**herapies (SWEDEHEART) study also examined sex-based outcomes after SAVR as a secondary analysis.[8] Although no differences were demonstrated, this trial did not balance the covariates between sexes, and the only outcome was survival. Finally, both trials also included patients undergoing coronary artery bypass grafting. Therefore, whether outcomes after isolated SAVR are similar for males vs females, and whether SAVR differentially impacts outcomes related to quality of life, is unknown.

The objective of this study was to evaluate real-world outcomes after SAVR in male and female patients. We hypothesized that survival and HF may differ based on sex. If such a difference is demonstrated, it would support work to identify opportunities for sex-specific strategies related to valve choice, postoperative monitoring, and pharmacotherapy in patients undergoing SAVR.

Received for publication October 24, 2022. Accepted December 2, 2022.

Ethics Statement: The data from this study are held securely at ICES (formerly the Institute for Clinical Evaluative Sciences). ICES is an independent, nonprofit research institute with a legal status under Ontario's health information privacy law that allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. The use of data is authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board (see link to ICES Data and Privacy at www.ices.on.ca).

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See page 227 for disclosure information.

Methods

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Design and study population

We conducted a population-based, retrospective cohort study in Ontario, Canada, identifying patients using the CorHealth Ontario clinical registry (formerly the Cardiac Care Network of Ontario Cardiac Registry). Adult patients (aged $\geq$ 18 years) were included if they underwent isolated SAVR with or without ascending aortic replacement between October 1, 2008, and September 31, 2019. Patients undergoing other concomitant surgery (eg, coronary artery bypass grafting, mitral, tricuspid, or pulmonic valve), aortic valve repair, TAVI, aortic surgery (distally or involving the arch), aortic root surgery (Bentall, homograft, or Ross procedure) were excluded, as were patients undergoing surgery for endocarditis within 30 days of the procedure. We also excluded patients with the following: invalid or missing ICES key number, birth date, or sex; non-Ontario residence or noneligibility under the Ontario Health Insurance Plan (OHIP) at index surgery date; residency in long-term care homes; and missing valve type.

Data sources

CorHealth Ontario maintains a detailed prospective registry of all patients from the 11 institutions in Ontario, Canada where SAVR surgery is performed. The registry captures demographic, comorbidity, and procedural-related information and has been validated through selected chart audits and in multiple studies.[9-12] Data have been complete since October 1, 2008. The registry was used to obtain all aortic valve replacement surgeries. Valve type was assigned as being tissue, mechanical, or missing, using CorHealth Ontario records. This information was linked with the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), and missing valve types were supplemented with CIHI DAD data using intervention codes to determine valve type.

We used the clinical registry data from CorHealth Ontario, and population-level administrative healthcare databases with information on all Ontario residents. Administrative databases were linked deterministically, by using encrypted, unique, confidential codes that preserve patient confidentiality, and were analyzed at ICES.

The following were linked: (i) the CorHealth Ontario registry (date of cardiac procedure, outcomes, comorbidities, covariates); (ii) CIHI DAD, which captures all admissions (outcomes, comorbidities; (iii) the Same Day Surgery (SDS) Database (outcomes, comorbidities); (iv) the National Ambulatory Care Reporting System (NACRS) database (comorbidities and all emergency department visits); (v) the Ontario Mental Health Reporting System database (comorbidities); (vi) the OHIP database, which captures operative details (on/off pump), number of grafts, comorbidities, and covariates; (vii) the Registered Persons Database (RPDB), which captures all deaths for residents of Ontario; (viii) the Continuing Care Reporting System (outcomes); and (ix) the Canadian Organ Replacement Register (CORR; covariates). These administrative databases have been validated for many outcomes, exposures, and comorbidities, including HF, chronic obstructive pulmonary disease, asthma, hypertension, myocardial infarction, dementia, and diabetes.[13]

Comorbidities

Diagnoses of aortic stenosis and aortic insufficiency were derived from the CIHI DAD if they were not present in the CorHealth Ontario data. Comorbidities were identified from the CorHealth Ontario registry and were supplemented with data from the CIHI DAD, the SDS Database, the NACRS database, the CORR, the RPDB, and the OHIP, using International Classification of Diseases 10th Revision, Canadian (ICD-10-CA) codes,[14] as well as OHIP fee codes, intervention codes, and treatment codes from within 5 years prior to the index procedure.[15,16] Left ventricular ejection fraction was derived from CorHealth Ontario data and categorized as being either class 1 ($>$ 45%), class 2 (36%-45%), class 3 (25%-35%), or class 4 ($<$ 25%).[17] Socioeconomic status was estimated based on patients' neighborhood median income in the Canadian census, and their residence (rural vs urban) was determined using definitions from Statistics Canada.[18] Procedural urgency was ascertained from the CorHealth Ontario registry and OHIP codes. Height, weight, and body mass index were identified from the CorHealth Ontario registry.[19-21]

Outcomes

The primary outcome was all-cause mortality, obtained from the RPDB. Secondary outcomes included endocarditis, major thromboembolic or hemorrhagic events, major adverse cerebral and cardiovascular events (MACCE, defined as the composite of myocardial infarction hospitalization, repeat aortic valve surgery/reintervention, HF hospitalization, and stroke) and patient-derived adverse cardiovascular and noncardiovascular events (PACE, defined as the composite of the following; severe stroke, new-onset congestive HF [CHF], new-onset dialysis, ventilator dependency, and nursing home admission),[22] and each of the individual MACCE and PACE. Stroke, myocardial infarction, and CHF hospitalizations were identified by linking to the CIHI-DAD using validated diagnostic code algorithms that have high sensitivity and specificity.[23-29] Repeat aortic intervention, including TAVI, SAVR, and balloon valvuloplasty, was identified using CorHealth Ontario data.[13,24,30] Hemorrhagic events included any episode of major internal or external bleeding that caused death, hospitalization, or permanent injury (eg, vision loss) or necessitated transfusion. These algorithms have been validated previously.[31-33] Endocarditis incidence was collected from the CIHI DAD.[34] Dialysis incidence was collected from the CIHI DAD, the OHIP, and the CORRdatasets.[22,32] Severe stroke requiring hospitalization was identified in the CIHI DAD and

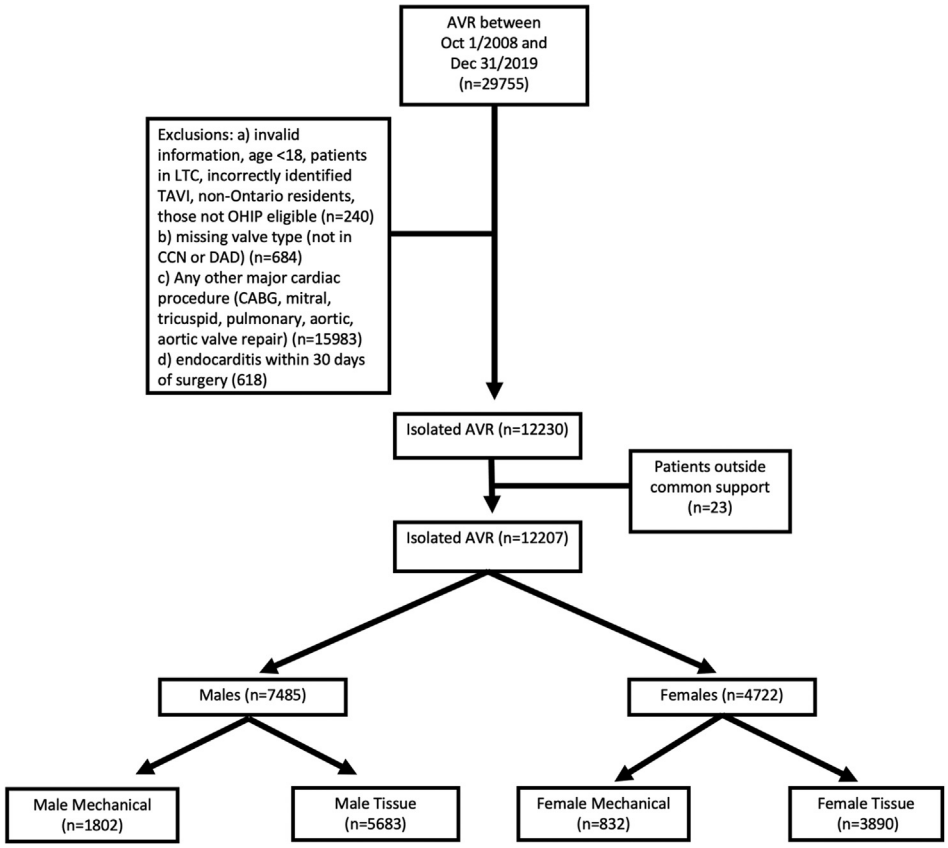

Figure 1. Patient flow. AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CCN, Cardiac Care Network; DAD , Canadian Institute for Health Information Discharge Abstract Database; Dec, December; LTC, long-term care; Oct, October; OHIP, Ontario Health Insurance Plan; TAVI, transaortic valve implantation.

the National Rehabilitation Reporting System database using a validated algorithm with 70% sensitivity and 99% specificity.[24,35] New-onset HF was identified in the CIHI DAD, the OHIP, the NACRS, the Ontario Mental Health Reporting System, and the SDS datasets. Nursing home admission incidence was collected from the Continuing Care Reporting System dataset, whereas incidence of ventilator dependence was collected from the OHIP dataset. The date of last follow-up was March 30, 2020.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) or median (interquartile range [IQR]), and categorical variables were expressed as number (proportion). Multiple imputation by fully conditional specification was used for 6 categorical and 2 continuous variables, with missing $\leq$ 10%. Ten imputations were used in the modeling. After the stability of the results was verified across imputations, the first imputation was used for all graphs. Baseline characteristics of male vs female patients in the overall sample were compared using the Student t test and the χ^2 test, for continuous and categorical variables, respectively. The Kruskal-Wallis test was used to test for normality.

To assess the effect of sex on outcomes after SAVR, we developed a nonparsimonious multivariable logistic regression model to estimate a PS, using sex as the dependent variable, and the characteristics listed in Supplemental Table S1 as covariates. Stabilized inverse PSs were developed as weights for each patient (inverse probability of treatment weighting [IPTW]),[36] by dividing by the crude proportion in each group.[37] Analysis was restricted to patients in zones of common support based on the propensity distribution.[38] After weighting, between-group imbalances were considered to be small if the absolute standardized difference for a given covariate was $<$ 10%.[39] Patients were censored if they became nonresidents of the province of Ontario. Event time was defined as the period from the date of index surgery until the date of the event or, if censored, the date of the last follow-up.

Mortality rates were assessed using a Cox proportional hazard model in the weighted samples. To account for death as a competing event, we estimated the cumulative incidence of each of the secondary outcomes by using cumulative incidence functions, and we assessed for significance of differences between groups using the Fine and Gray test of inequality.

The measure of association was hazard ratios (HRs) with 95% confidence intervals. The proportionality assumption was tested by analyzing Schoenfeld residuals. If the assumption was violated, time-dependent HRs were reported. Analyses were performed using SAS Enterprise Guide, version 7.1 (SAS Institute, Cary, NC), with statistical significance defined by a 2-sided P of $<$ 0.05.

Table 1. Covariates and standardized differences (StdDif) of male and female patients undergoing aortic valve replacement (AVR) before and after inverse proportion treatment weighting (IPTW)

Variable	Before, male	Before, female	Before, StdDif	After, male	After, female	After, StdDif
Sample N	7485	4722		12,302	12,359	
Index year	2014.1	2013.8	0.074	2014	2014	0.002
Valve type—mechanical	24.1	17.6	0.159	22.3	22.3	0.001
Valve type—tissue	75.9	82.4	0.159	77.7	77.7	0.001
Age, y	65.4	69.7	0.365	66.8	66.5	0.022
Income quintile						
1	16.6	18.6	0.053	17.6	17.3	0.006
2	19.8	21.1	0.033	20.5	20.7	0.006
3	20.9	20.3	0.016	20.6	20.7	0.004
4	20.9	20.3	0.014	20.8	20.2	0.014
5	21.8	19.7	0.053	20.6	21.1	0.010
Rural	17.6	16.6	0.026	17.7	18.4	0.018
Hospital type community	20.8	21.9	0.027	21.0	21.1	0.002
Hospital type teaching	79.2	78.1	0.027	79.0	78.9	0.002
Atrial fibrillation	16.5	17.5	0.025	16.8	16.1	0.019
Asthma/COPD	29.7	34.7	0.107	31.6	32.6	0.021
Hypertension	78.0	82.4	0.110	79.4	79.0	0.011
Diabetes	31.0	31.9	0.019	31.4	32.3	0.019
CHF	35.4	38.5	0.066	36.4	36.5	0.002
MI	9.1	6.9	0.082	8.2	8.7	0.019
LVEF Category						
1	82.8	91.3	0.254	86.0	86.0	0.002
2	11.7	6.4	0.186	9.8	9.5	0.008
3	4.9	2.1	0.156	3.8	4.1	0.011
4	0.6	0.3	0.043	0.4	0.4	0.007
eGFR, mL/min	93.7	76.7	0.496	88.9	90.3	0.034
Emergency procedure	7.2	5.3	0.076	6.6	7.5	0.037
Aortic surgery with SAVR	28.9	24.4	0.102	26.6	26.7	0.002
Aortic stenosis	86.8	94.8	0.280	89.7	89.6	0.001
Aortic regurgitation	27.7	15.8	0.291	23.4	23.0	0.009
CCS classification						
0	62.7	61.0	0.036	61.8	61.5	0.006
I	13.7	14.3	0.018	14.1	14.1	0.001
II	11.7	11.8	0.002	11.8	11.9	0.002
III	5.7	7.1	0.059	6.0	6.1	0.002
IV	0.8	1.0	0.019	0.9	0.9	0.002
e	1.1	0.8	0.036	1.0	1.4	0.036
h	0.4	0.4	0.003	0.5	0.5	0.003
i	1.6	1.5	0.007	1.5	1.4	0.010
l	2.3	2.2	0.007	2.4	2.3	0.004
NYHA classification						
1	39.8	32.6	0.151	37.3	37.9	0.013
2	32.2	32.0	0.006	31.8	31.9	0.002
3	24.6	31.3	0.151	27.3	26.3	0.024
4	3.4	4.1	0.039	3.6	3.9	0.017
Hyperlipidemia	52.3	52.3	0.002	52.3	51.4	0.017
Smoker, current	16.1	10.6	0.163	14.0	14.5	0.012
Smoker, former	37.0	23.8	0.289	32.2	31.8	0.010
Smoker, no	46.9	65.6	0.383	53.8	53.8	0.001
Peripheral vascular disease	12.2	10.4	0.059	11.5	11.6	0.004
Cerebrovascular disease	8.7	9.6	0.033	9.8	9.2	0.021
Liver disease	1.2	0.9	0.026	1.0	1.0	0.002
Paraplegia/Hemiplegia	0.3	0.4	0.017	0.7	0.5	0.030
Venous thromboembolism	0.7	0.6	0.002	0.7	0.8	0.015
Chronic renal disease	3.8	2.8	0.055	3.3	3.3	0.003
Dialysis	1.4	0.9	0.046	1.3	1.3	0.008
PCI	6.7	4.2	0.110	5.9	5.9	0.003
Ischemic heart disease	15.9	14.3	0.046	15.3	15.5	0.004
Hypothyroidism	0.6	2.6	0.160	1.4	1.4	0.000
Primary cancer	4.3	3.7	0.035	4.2	4.2	0.002
BMI, kg/m^2	29.7	30.0	0.035	32.1	30.7	0.082
Anemia	6.5	9.1	0.095	7.6	7.5	0.003
Alcohol abuse	1.5	0.6	0.093	1.1	1.0	0.007
Psychosis	0.2	0.3	0.006	0.2	0.3	0.006
Depression	0.8	1.4	0.052	1.0	0.9	0.005
Previous cardiac surgery	6.8	4.3	0.105	5.7	5.9	0.006

Table 1. Continued.

Variable	Before, male	Before, female	Before, StdDif	After, male	After, female	After, StdDif
Frailty risk score	1.4	1.7	0.078	1.6	1.5	0.012

Values are %, unless otherwise indicated. Index year—average year of surgical AVR (SAVR). Canadian Cardiovascular Society (CCS) classes: 0 = asymptomatic; I = normal activity; II = slightly limited; III = markedly limited; IV = symptoms at rest; e = emergent; h = high risk; I = intermediate risk; l = low risk. New York Heart Association (NYHA) classes: 1 = asymptomatic; 2 = slightly limited; 3 = markedly limited; 4 = symptoms at rest.

BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Sensitivity analysis

To address the potential of a valve-type-age interaction effect on outcomes, a multivariable Cox proportional hazard regression model that adjusted for the same baseline covariates as our PS model was applied for each sex, with a valve-type-age interaction term included with age as a categorical variable (each decade).

Results

Patient flow is presented in Figure 1. The baseline demographics of all male and female patients included are presented in Supplemental Table S1. Female patients were older, with a greater incidence of chronic obstructive pulmonary disease, hypertension, CHF, aortic stenosis, and anemia, with higher frailty and worse renal function. Male patients more frequently underwent mechanical valve replacement and had higher incidences of emergency surgery, smoking, and reoperative surgery. Median follow-up in male patients was 5.2 years (IQR, 2.9, 7.9), and in female patients, it was 5.2 years (IQR, 3.1, 8.1; P = nonsignificant). PS density plots of patients before and after IPTW are shown in Supplemental Figure S1. Standardized differences before and after IPTW are presented in Table 1.

Table 2. Secondary outcomes in male and female patients undergoing surgical aortic valve (AV) replacement with reference male sex

Outcome	HR (95% CI)	P
Repeat AV surgery/intervention	0.863 (0.484, 1.539)	0.609
Major hemorrhagic or thromboembolic events	0.935 (0.824, 1.061)	0.297
Endocarditis	0.876 (0.635, 1.208)	0.419
MACCE	1.035 (0.880, 1.219)	0.672
PACE	1.121 (0.997, 1.260)	0.056
MACCE or PACE	1.065 (0.958, 1.184)	0.246
Severe stroke	0.925 (0.686, 1.246)	0.607
Ventilator-dependence	0.621 (0.185, 2.083)	0.440
New-onset CHF	1.211 (1.051, 1.394)	0.008
New LTC	1.118 (0.913, 1.371)	0.280
Dialysis	0.689 (0.488, 0.974)	0.035
MI	1.082 (0.801, 1.462)	0.609
CHF hospitalization	1.200 (1.036, 1.390)	0.015
Stroke	0.888 (0.668, 1.181)	0.411

Analysis was completed using inverse probability treatment weighting to balance groups with 10 sets of imputation.

CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; LTC, long-term care; MACCE, major adverse cerebral and cardiovascular events; MI, myocardial infarction; PACE, patient-derived adverse cardiovascular and noncardiovascular events.

Outcomes and numbers of patients censored prior to IPTW are presented in Supplemental Table S2. The unadjusted rate of all-cause mortality in the total cohort is presented in Supplemental Figure S2. Female patients had a significantly worse rate of survival overall ($P = 0.0003$). All-cause survival was significantly increased in patients undergoing mechanical as opposed to tissue valve surgery in both male and female patients ($P < 0.001$; Supplemental Fig. S3).

After applying IPTW, all-cause mortality did not differ significantly between male and female patients (HR 0.949, 95% confidence interval [0.851-1.059]). Time-dependent HRs for all-cause death are presented in Supplemental Table S3. The groups were not statistically different at any time point.

Secondary outcomes between the 2 groups are presented in Table 2. Female sex was associated with a significantly increased risk of new-onset CHF ($P = 0.008$) and CHF hospitalization ($P = 0.015$). PACE incidence was not statistically significantly different between sexes ($P = 0.056$; Fig. 2A and B). Male sex was associated with an increased risk of new-onset dialysis ($P = 0.035$; Fig. 3).

In 3 of the secondary outcome measures (repeat aortic valve intervention, severe stroke, and stroke), potential deviations of the proportional hazards assumption were present, based on Schoenfeld residual assessment. These outcomes were further analyzed for time-dependency, and no significant differences were identified.

Sensitivity analysis

The interaction term of age category and valve type was tested for the outcomes of new-onset CHF and CHF hospitalizations. The interaction effect was not significant in either male or female patients (Table 3).

Discussion

This large population health study has demonstrated significant disparities in the outcomes for male vs female patients after SAVR. The 2 groups did not differ in the primary outcome of freedom from all-cause mortality at a maximum of 10 years. Female sex was associated with an increased risk of new-onset CHF and CHF hospitalization. Male sex was associated with an increased risk of new-onset dialysis, despite a higher preoperative estimated glomerular filtration rate. These latter 2 findings should be considered exploratory.

Several studies have addressed sex differences in outcomes after SAVR. These studies have confirmed that female patients have an increased perioperative risk,[40] but no convincing evidence has been found of differences in medium-term outcome in terms of survival.[7,8,41,42] Even taking these

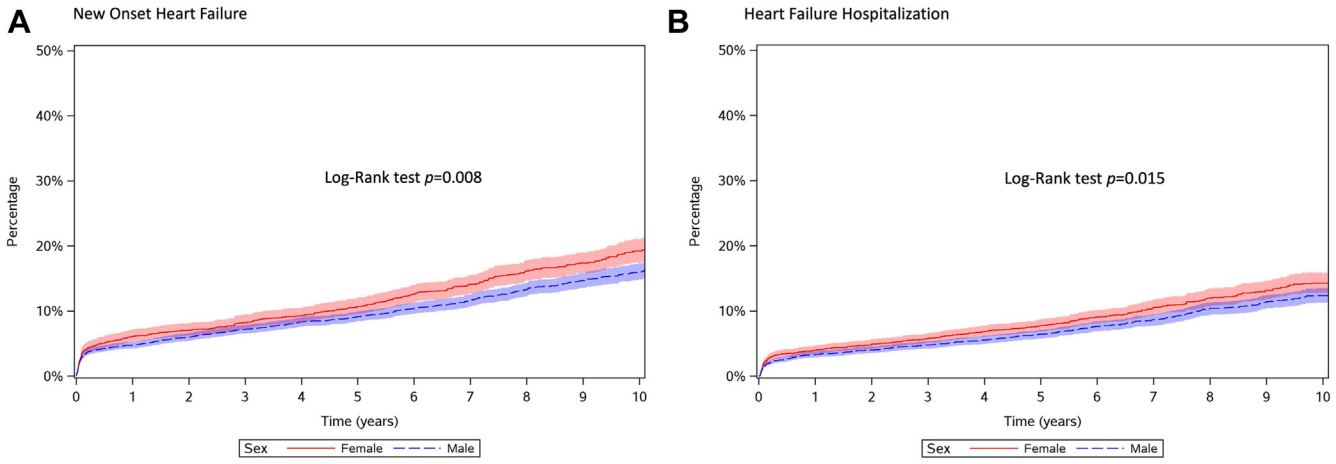

Figure 2. Weighted cumulative incidence function curves by sex for (**A**) new-onset congestive heart failure and (**B**) congestive heart failure hospitalization in maless and females undergoing isolated surgical aortic valve replacement. First imputation utilized in derivation. Significance of differences between groups tested using the Fine and Gray test of inequality.

findings into account, equating "equivalent" survival after SAVR as being representative of a positive health outcome in female patients reflects a false logic. In the population without heart disease, female patients have greater longevity by up to 4 years,[43] and thus, equivalency in survival to male patients would imply a significant disadvantage that has not been considered previously.

Sex has not been considered previously as a potential contributor to HF after SAVR despite the presence of key phenotypic differences that may predispose patients to HF.[44-46] Female patients present more frequently with paradoxic low-flow, low-gradient aortic stenosis,[47] and the incidence of HF with preserved ejection fraction is also higher in female patients.[48,49] Recognition of this disorder is particularly important postoperatively, as renin-angiotensin system inhibitors may have a greater effect postoperatively, compared to results in patients with HF with reduced ejection fraction.[50]

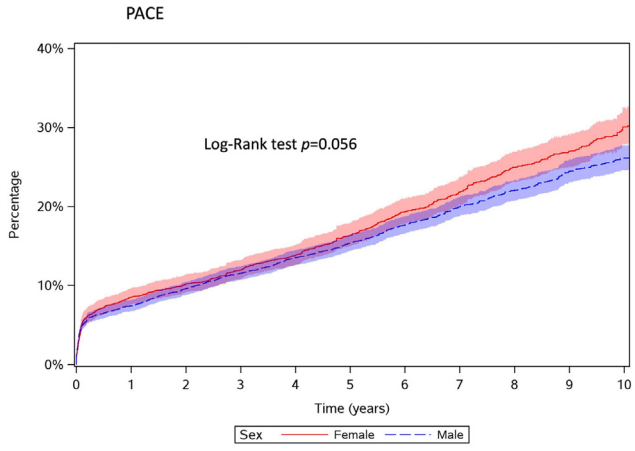

Figure 3. Weighted cumulative incidence function curve by sex for patient-derived adverse cardiovascular and noncardiovascular events (PACE). First imputation was utilized in the derivation. Significance of differences between groups was tested using the Fine and Gray test of inequality.

These agents may induce regression of left ventricular hypertrophy, which has been associated with improved clinical outcomes.[51]

Another factor that can influence early and long-term outcomes such as CHF after SAVR is patient-prosthesis mismatch. This issue has been shown to be more common in female patients,[52] likely owing to smaller annulus size.[53,54] Chen et al., in a review of 14 observational studies of 15,000 patients after SAVR, demonstrated that patient-prosthesis mismatch is a predictor of worse mid- and long-term survival outcomes, an effect seen most prominently in younger patients and female patients.[55]

The current study has demonstrated an association between male sex and the need for new postoperative dialysis. This finding is consistent with results of Chaker et al. who examined outcomes in 28,237 matched pairs of male and female patients undergoing SAVR reported in the Nationwide Inpatient Samples Study.[40] Although the incidence of dialysis was similar in the groups, the incidence of acute kidney injury was significantly higher in male patients (16.6% vs 14.3%, $P < 0.0001$). Our trial did not measure acute kidney injury that does not require dialysis, as these data from administrative datasets may be less reliable; therefore, the relationship of acute injury to acute injury that requires dialysis is not currently known.

Several significant limitations have import for the interpretation of these findings. We recognize that the follow-up reflects only medium-term outcomes, and an effect of structural valve disease is likely and might be reflected with longer follow-up. This study also has not considered the dramatic effect of TAVI on outcomes related to aortic valve replacement. Female patients appear to have a greater incidence of procedural complications and stroke with TAVI, but they may have better long-term survival outcomes compared to male patients.[56] We do not know what the impact of novel technological innovations, such as valve-in-valve implantation, will be in terms of the overall survival in younger age groups, and the potential impact of sex on these outcomes. We have elected to include patients who have undergone concomitant ascending aortic replacement, as we felt that this procedure

Table 3. Assessment of valve type-age category interaction on the secondary outcomes of new-onset congestive heart failure (CHF) and CHF hospitalization

Secondary outcome	Age category, y	Male		Female	
		HR (95% CI)	*P*	HR (95% CI)	*P*
New-onset CHF	50−54	1.041 (0.421, 2.581)	0.929	0.890 (0.246, 3.234)	0.858
	55−59	1.064 (0.474, 2.387)	0.880	0.656 (0.206, 2.084)	0.474
	60−64	0.788 (0.357, 1.740)	0.556	1.009 (0.347, 2.940)	0.987
	65−69	0.752 (0.326, 1.736)	0.504	1.414 (0.516, 3.879)	0.501
	70−74	0.636 (0.246, 1.649)	0.352	1.723 (0.587, 5.057)	0.322
	75+	1.226 (0.555, 2.709)	0.615	1.537 (0.577, 4.090)	0.390
CHF hospitalization	50−54	0.637 (0.168, 2.411)	0.506	0.271 (0.031, 2.335)	0.235
	55−59	0.549 (0.165, 1.827)	0.328	0.215 (0.030, 1.554)	0.128
	60−64	1.300 (0.409, 4.135)	0.656	0.839 (0.141, 4.987)	0.847
	65−69	1.007 (0.327, 3.095)	0.991	0.880 (0.163, 4.751)	0.882
	70−74	2.033 (0.636, 6.500)	0.231	0.896 (0.156, 5.142)	0.902
	75+	0.825 (0.260, 2.621)	0.744	0.684 (0.127, 3.693)	0.659

Patients were stratified by sex; then analysis was performed with a multivariable Cox proportional hazard regression model, adjusted for the same baseline covariates as the propensity score model.

CI, confidence interval; HR, hazard ratio.

would not significantly impact major surgical decisions such as valve choice. We recognize that sex-based differences in outcomes after aortic surgery may be present.[57] Beller et al.[58] have demonstrated that female patients undergoing ascending aortic surgery have less favourable outcomes, compared to those of male patients ,with higher perioperative mortality and worsened long-term survival. However, significant differences in the comorbidity profile between sexes were not balanced as they were in the current study. Further, ascending aortic replacement was included as a covariate in the weighting process, and thus the impact of this factor should have been balanced. This study also analyzed multiple secondary outcomes that could introduce the risk of a type 1 error in the absence of correction for multiple testing, but these findings are exploratory and thus require confirmation via more-complete analysis.

The use of propensity methods to generate 2 SAVR groups (male and female), for comparison of outcomes, violates the exchangeability assumption. However, the applicability of balancing scores to natural experiments such as this one is well established.[59] Statistical processes used in developing a balancing score in such settings are identical to those used in developing PSs.[60] This strategy has been successfully used in other surgical studies such as the comparison of outcomes after aortic root surgery in patients with tricuspid and bicuspid valves.[61]

Finally, although we demonstrated an increase in the incidence of HF in female patients after SAVR, this was a secondary outcome. Therefore, the finding is only hypothesis-generating and should be confirmed with further prospective studies specifically analyzing this question.

Conclusion

In this large population-based study of outcomes after SAVR, we have demonstrated that no sex-based differences in survival are present. Sex-related differences in HF and dialysis may be present, but these findings are exploratory and require further study. These findings could be basis research from which to evaluate the role of optimized sex-specific medical therapy to prevent complications following SAVR, and they support the integration of patient-centric outcome measurement and sex differences in cardiovascular clinical trials.

Acknowledgements

The authors acknowledge that the clinical registry data used in this publication is from participating hospitals through CorHealth Ontario, which serves as an advisory body to the Minister of Health and Long-Term Care (MOHLTC), is funded by the MOHLTC and is dedicated to improving the quality, efficiency, access and equity in the delivery of the continuum of adult cardiac, vascular and stroke services in Ontario, Canada. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed in the material are those of the authors and not necessarily those of CIHI.

Funding Sources

The authors acknowledge support from an operating grant from the Oracle Pilot Funding Initiative at the University of Ottawa Heart Institute. This study was supported by ICES which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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