Predictors of Long-term Cardiovascular Versus Non-cardiovascular Mortality and Repeat Intervention in Patients Having Transcatheter Aortic Valve Implantation

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There is a paucity of literature characterizing the risk of long-term mortality and reintervention after transcatheter aortic valve implantation (TAVI). Addressing this gap has become increasingly relevant with the inclusion of intermediate and low surgical risk patients and the need for data to inform their long-term management. We sought to investigate the long-term trends and predictors of cardiovascular versus noncardiovascular mortality as well as reintervention in post-TAVI patients. Our cohort consisted of 5,406 patients who underwent TAVI in Ontario, Canada from 2011 to 2018. We used Kaplan-Meier analysis to estimate 7-year all-cause mortality and a Cox proportional hazard model to identify demographic, co-morbid, and procedural predictors. Similarly, cumulative incidence functions were used to estimate cardiovascular versus noncardiovascular mortality at 5 years, with predictors identified through Fine-Gray models. The Kaplan-Meier estimate for 7-year all-cause mortality in our cohort was 67%; this was driven by a number of co-morbidities including congestive heart failure and liver disease. We found that cardiovascular death was more likely for approximately the first 2 years post-TAVI whereas noncardiovascular death was more likely from this point to the end of the study. We identified a number of factors that uniquely modified the risk of either cardiovascular or noncardiovascular mortality. Only 1.6% of patients who underwent repeat intervention. The distinct factors associated with cardiovascular versus noncardiovascular death suggest different approaches to short-term and long-term surveillance of patients post-TAVI by both the heart team and primary care providers. **© 2020 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2020;135:105−112)**

Over the last decade, transcatheter aortic valve implantation (TAVI) has transformed the therapeutic options available for managing severe aortic stenosis. As outcomes continue to improve, understanding the cause and predictors of long-term mortality has become increasingly important. Although a number of studies have investigated specific causes of death for patients having undergone TAVI, the follow-up period of these studies is typically 30 days and 1 year.[1,2,3] Moreover, the literature on long-term outcomes focuses on all-cause mortality.[4,5] There has been an improvement in this metric, from a 5-year all-cause mortality rate of 71.8% in a cohort recruited from 2007 to 2009, to a mortality of 48.3% in a cohort recruited from 2010 to 2012.[4,6] This general reduction in mortality is multifactorial and due, in part, to the expansion of TAVI to those at intermediate and low surgical risk.[7,8,9] These findings suggest that an appreciable proportion of patients will survive with functional valves beyond 5 years but there is a paucity of long-term data on cause-specific mortality. This data would provide important insights into modifiable factors that could impact long-term management of this growing group of patients. Our specific objectives were to identify and contrast factors associated with cardiovascular versus noncardiovascular mortality, as well as rates of reintervention. Our hypothesis was that there would be a higher

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See page 110 for disclosure information.

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likelihood of cardiovascular death compared with noncardiovascular death initially post-TAVI due to periprocedural complications but that this relationship would reverse with longer follow-up.

Methods

The use of data in this retrospective cohort study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. The use of anonymized administrative data without patient consent at ICES is allowed in Ontario on the basis of provincial privacy legislation. We have adhered to the STROBE statement for reporting of observational studies.

Ontario is the largest province in Canada with a population of 14.2 million. All residents have universal access to health care and hospital services through a publicly funded health care program administered by a single third-party payer, the Ontario Ministry of Health and Long-Term Care. Although TAVI has been available in Ontario since 2007, funding was first approved by the Ontario Ministry of Health and Long-Term Care in September 2012.

Our study utilized data collected in the CorHealth Ontario TAVI Registry. The TAVI Registry contains demographic, co-morbidity and procedural variables from the 11 tertiary cardiovascular centers across the province of Ontario that perform TAVI, with data entry as a mandatory prerequisite for provincial funding. These data elements have been validated through selected chart abstractions and core laboratory analyses.[10]

We used the Canadian Institute for Health Information Discharge Abstract Database to generate baseline co-morbidity and procedural data. The CorHealth registry and Canadian Institute for Health Information Discharge Abstract Database were used to determine repeat TAVI and SAVR procedures. Validated ICES-derived databases were used to identify diabetes,[11,12] congestive heart failure (CHF),[13] hypertension,[14,15] dementia,[16] and chronic obstructive pulmonary disease.[17] Medical frailty was defined using the hospital frailty risk score.[18] Mortality was ascertained through the Registered Persons Database, as were additional demographic variables such as rural residence and neighbourhood income quintile. We used the Office of the Registrar General—Deaths database to establish cause of death as cardiovascular (see Appendix Table 1) or noncardiovascular, defined as all

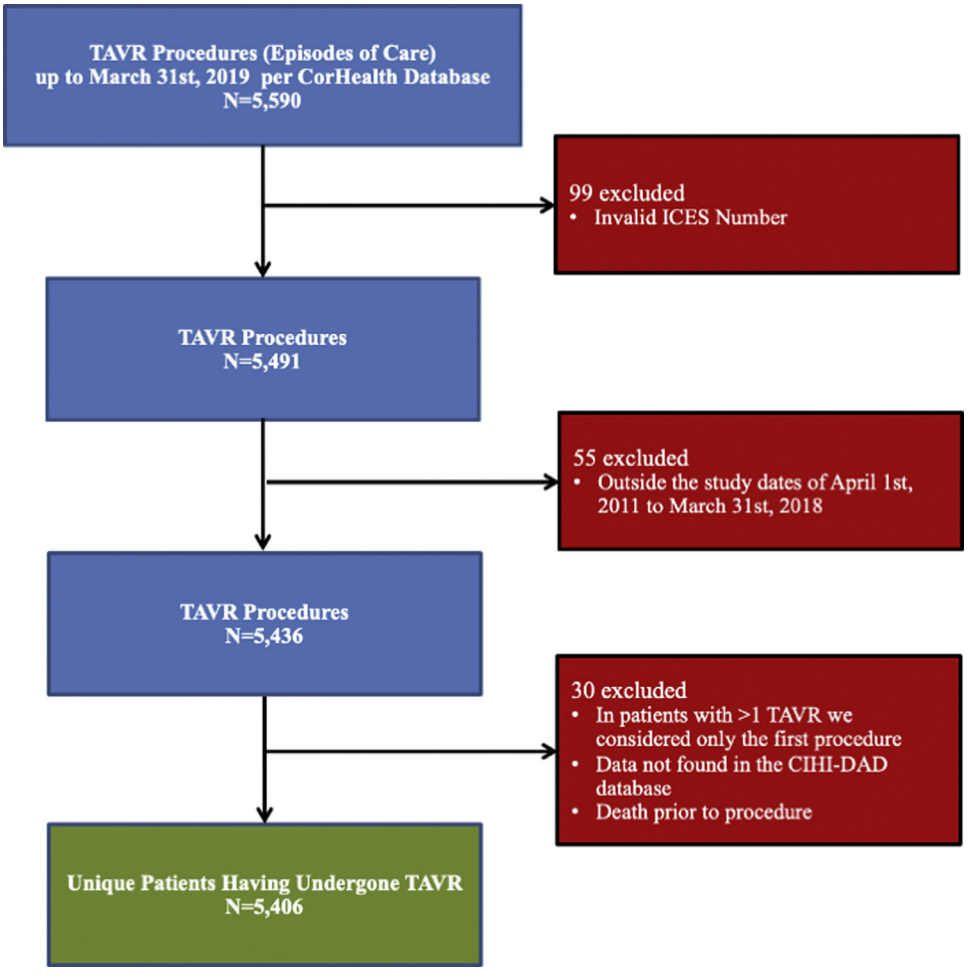

Figure 1. Patient flow diagram and cohort creation. TAVI = transcatheter aortic valve replacement.

other causes of death. These datasets were linked using unique encoded identifiers and analyzed at ICES.

We included all TAVI procedures in Ontario from April 1st, 2011 to March 31st, 2018, a period during which data entry into the CorHealth registry was mandatory. As the Office of the Registrar GeneralDeaths only includes cause-specific mortality data up to the end of 2016, follow-up was limited to this date for cardiovascular and noncardiovascular mortality. We excluded patients with data quality issues. For patients with more than 1 TAVI procedure, we included the first procedure as the index event for this study.

Patients were followed from the date of TAVI for up to 8 years, to July 31, 2019. Our primary clinical outcomes were all-cause mortality, as well as cardiovascular versus noncardiovascular mortality. The secondary outcome was reintervention, defined as requiring repeat TAVI or surgical aortic valve replacement (SAVR) post-TAVI.

The probability of all-cause mortality was calculated using Kaplan-Meier method. The probability of cardiovascular versus noncardiovascular mortality was estimated by the cumulative incidence function. We modeled the cause-specific hazard of all-cause mortality using a Cox proportional hazard model. Multivariable models were adjusted for all baseline and procedural variables, which were chosen based on clinical relevance. Fine-Gray models were developed to model the subdistribution hazard of cardiovascular mortality and noncardiovascular mortality, treating other causes of death as a competing risk. A Fine-Gray model was also developed to model the sub-distribution hazard of repeat TAVI or SAVR, treating death as a competing risk. Cause-specific Cox proportional hazards models were generated for all outcomes as sensitivity analyses. All data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). Statistical significance was considered to be 2-sided p-values of <0.05.

Results

Our cohort consisted of 5,406 unique patients who underwent TAVI from April 1st, 2011 to March 31st, 2018, after the aforementioned exclusions (Figure 1). The mean age was 82.0 years, 44.6% of patients were female, and income quintile was fairly equally distributed (Table 1). The most common co-morbidities were hypertension (93.8%), ischemic heart disease (71.6%), and dyslipidemia (65.2%) (Table 1). Year over year, there was an increase in the number of TAVI performed, from 60 in 2011 to 1,369 in 2018. Our cohort had a median and mean follow-up of 822 and 664 days respectively, reflecting the growth in volumes in the more recent years.

The Kaplan-Meier estimate for mortality at 7 years was approximately 67% (Figure 2). Additionally, the Kaplan-Meier estimate for mortality at 5 years was approximately 51% (Appendix Figure 1). The unadjusted death by valve type is found in Appendix Table 2.

The cumulative incidence of cardiovascular mortality at 5 years was 21% compared with 29% for noncardiovascular mortality (Figure 3). We observed that patients were more likely to experience cardiovascular death than noncardiovascular death up to 1.8 years of follow-up. From 1.8 to 5 years, noncardiovascular death was more common. The breakdown of type of cardiovascular death by ICD-10 code is found in Appendix Table 3.

In terms of predictors of all-cause mortality (Table 2), we found that female gender was protective (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.74 to 0.91). S Co-morbidities including liver disease (HR 1.63, 95% CI

Table 1
Patient baseline characteristics

Baseline Characteristic	Total n = 5,406
Demographic characteristics	
Age (mean ± SD)	82.03 ± 7.43
Female	2,413 (44.6%)
Rural residence	590 (10.9%)
Income quintile	
1	1,056 (19.5%)
2	1,191 (22.0%)
3	1,108 (20.5%)
4	967 (17.9%)
5	1,074 (19.9%)
Medical co-morbidities	
Congestive heart failure	3,503 (64.8%)
CHF within 90 days of procedure	680 (12.6%)
Charlson score (mean ± SD)	1.92 ± 1.87
CAD/ischemic heart disease	3,869 (71.6%)
Cardiac arrhythmia	1,526 (28.2%)
Peripheral vascular disease	307 (5.7%)
Cerebrovascular disease	270 (5.0%)
COPD	1,898 (35.1%)
Dementia	357 (6.6%)
Cancer	385 (7.1%)
Dialysis	188 (3.5%)
Interstitial lung disease	77 (1.4%)
Liver disease	94 (1.7%)
Renal disease	522 (9.7%)
Diabetes	2,360 (43.7%)
Hypertension	5,069 (93.8%)
Dyslipidemia	3,523 (65.2%)
Frailty (mean ± SD)	3.22 ± 4.70
Prior cardiac procedure	
Coronary artery bypass graft	1,081 (20.0%)
Percutaneous coronary intervention	1,867 (34.5%)
Valve surgery	649 (12.0%)
Procedure characteristics	
Transfemoral access	4,594 (85.0%)
Non-transfemoral access	812 (15.0%)
Elective	4,531 (83.8%)
Urgent	875 (16.2%)
Valve type	
Balloon expandable	2703 (50.0%)
Self-expanding	1,523 (28.2%)
Missing	782 (14.5%)
Other	398 (7.4%)
Year of procedure	
2011	60 (1.1%)
2012	307 (5.7%)
2013	462 (8.5%)
2014	633 (11.7%)
2015	725 (13.4%)
2016	851 (15.7%)
2017	999 (18.5%)
2018	1,369 (25.3%)

CAD = coronary artery disease.

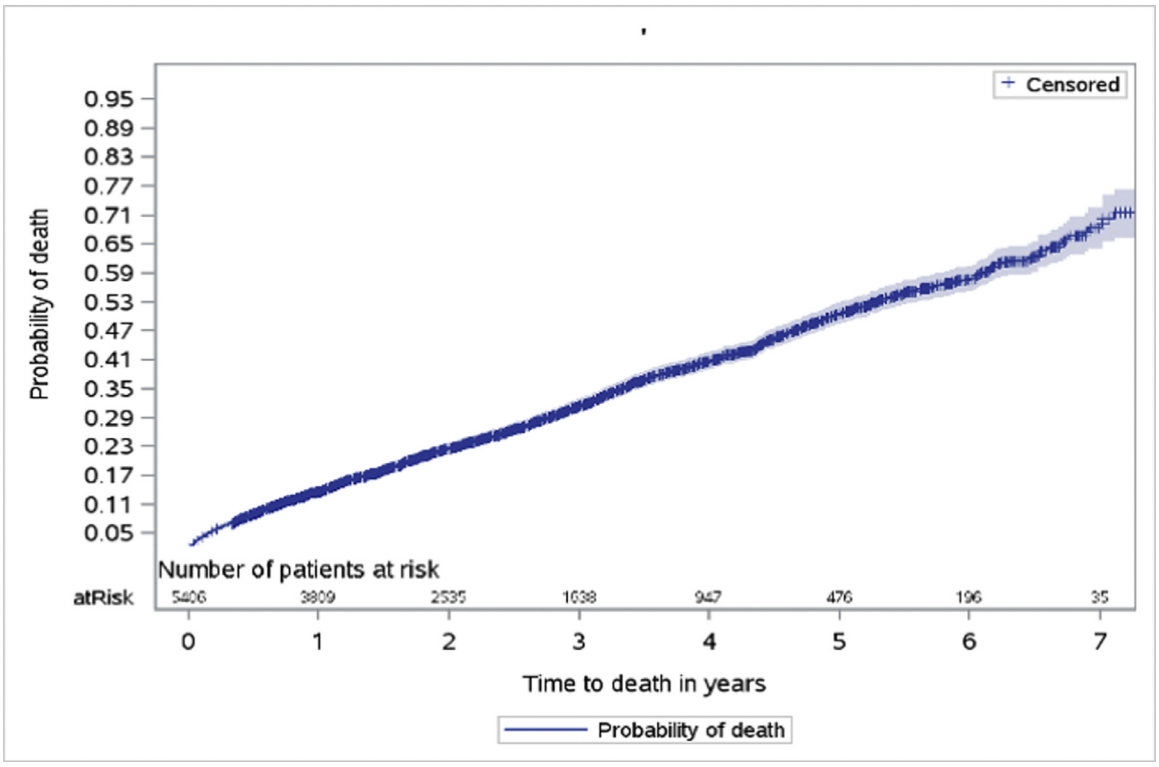

Figure 2. Kaplan-Meier curve for all-cause mortality from April 2011 to July 2019.

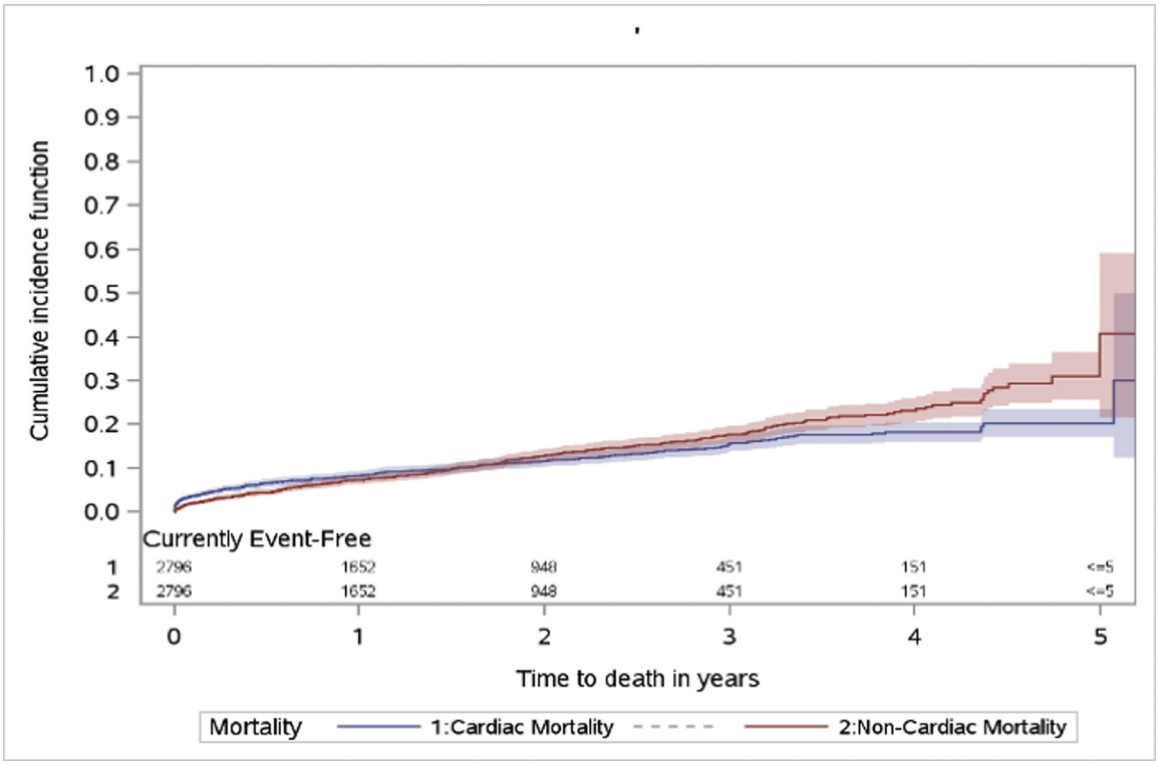

Figure 3. Cumulative incidence functions for cardiovascular and noncardiovascular death from March 2011 to December 2016.

1.17 to 2.26) and CHF (HR 1.43, 95% CI 1.26-1.62) were associated with increased mortality. Patients with transfemoral access TAVI (HR 0.72, 95% CI 0.64 to 0.82) had a reduced risk of death compared with alternative access patients, as did those with previous valve surgery (HR 0.82, 95% CI 0.70 to 0.95).

Table 2
Cause-specific Cox model for all-cause mortality from April 2011 to July 2019

Parameter	Hazard Ratio	95% CI	p-value
Age	1.03	1.02−1.04	<.0001
Charlson score	1.09	1.05−1.14	<.0001
Frailty score	1.03	1.02−1.04	<.0001
Female	0.82	0.74−0.91	0.0003
Rural residence	1.05	0.90−1.22	0.55
Transfemoral access	0.72	0.64−0.82	<.0001
Urgent procedure	1.17	1.04−1.32	0.01
Hypertension	0.97	0.78−1.22	0.82
Diabetes	1.14	1.02−1.28	0.03
Congestive heart failure	1.43	1.26−1.62	<.0001
Chronic obstructive pulmonary disease	1.25	1.13−1.38	<.0001
Arrhythmia	1.30	1.17−1.44	<.0001
Cancer	1.02	0.83−1.24	0.88
Coronary artery disease/ Ischemic heart disease	1.06	0.94−1.20	0.35
Cerebrovascular disease	0.91	0.74−1.12	0.37
Peripheral vascular disease	1.29	1.08−1.55	0.0053
Dementia	1.15	0.97−1.37	0.11
Dialysis	1.42	1.14−1.78	0.0021
Dyslipidemia	0.87	0.78−0.96	0.01
Liver disease	1.63	1.17−2.26	0.0037
Interstitial lung disease	1.25	0.89−1.75	0.19
Renal disease	0.98	0.82−1.16	0.82
Percutaneous coronary intervention	0.89	0.79−0.99	0.03
Previous coronary artery bypass graft	0.85	0.74−0.97	0.01
Previous valve surgery	0.82	0.70−0.95	0.01
Income quintile			
1	1.08	0.92−1.26	0.35
2	1.06	0.91−1.23	0.44
3	0.97	0.84−1.14	0.74
4	0.97	0.83−1.14	0.71
5 (reference)	1.00	N/A	N/A

With respect to predictors of cause-specific mortality (Table 3), we found that transfemoral access TAVI was associated with a lower hazard for both cardiovascular (HR 0.70, 95% CI 0.53 to 0.92) and noncardiovascular mortality (HR 0.73, 95% CI 0.56 to 0.94). Drivers of cardiovascular death included urgent procedure status (HR 1.44, 95% CI 1.10 to 1.87), and CHF (HR 1.52, 95% CI 1.09 to 2.11). Other drivers of cardiovascular mortality were age and Charlson score. Conversely, chronic obstructive pulmonary disease (HR 1.29, 95% CI 1.04 to 1.61) was associated with an increased risk of noncardiovascular mortality. Other drivers of noncardiovascular mortality were age and frailty score. Finally, female sex (HR 0.70, 95% CI 0.55 to 0.89) as well as previous percutaneous coronary intervention (HR 0.64, 95% CI 0.50 to 0.81) and coronary artery bypass graft (HR 0.70, 95% CI 0.52 to 0.94) were all associated with a reduced likelihood of noncardiovascular death alone. The sensitivity analyses using a cause-specific Cox model qualitatively showed the same predictors for cardiovascular and noncardiovascular death (Appendix Table 4).

As of July 31st, 2019, 86 (1.6%) of patients in our cohort had repeat intervention either in the form of TAVI or SAVR. To provide context, 6.2% underwent subsequent percutaneous coronary intervention. Older age and female gender were predictors of less repeat intervention with TAVI/SAVR (Table 4).

Discussion

In this population-based study of long-term mortality post-TAVI in Ontario, Canada, we found that all-cause mortality at 7 years was 67%. Predictors of all-cause mortality included co-morbidities such as CHF and liver disease. Cardiovascular death was more likely early post-TAVI, with noncardiovascular death more common in the long term

Previous studies have reported 5-year cardiovascular mortality rates of 53.1% for the PARTNER 1 cohort recruited from 2007 to 2009 and 39.7% for the CoreValve cohort recruited from 2011 to 2012.[19,20] Additionally, a systematic review in 2017 reported an aggregated 7-year all-cause mortality rate of 72%.[5] There have been considerable advances in the design of TAVI valves themselves and work assessing the durability of these prostheses has found that only 8.7% to 13.3% experience moderate structural deterioration at 5 to 6 years of follow-up.[21,22] These findings taken together further support the notion that an appreciable proportion of patients will survive with functional valves by 5 years and beyond.

Our work builds on previous publications through a number of novel findings. First, we have demonstrated an improvement in long-term mortality compared with previous cohorts. Although this likely reflects improvements in prosthetic technology and the TAVI procedure itself, previously reported values may have been increased due to a higher proportion of high-risk patients. In contrast, our cohort included more contemporary TAVI patients, a proportion of whom were likely in the intermediate risk category. Second, our most unique finding is the temporal pattern of early versus long term cause of death. We hypothesize that the early cardiovascular deaths were in part from early complications, whereas the late noncardiovascular deaths were driven by co-morbidities. Finally, while the low rate of reintervention could be interpreted as a reflection of the TAVI durability, the reduced risk with age indicates that older patients are likely not living long enough to require reintervention.

We have identified a number of risk factors that were uniquely associated with either cardiovascular versus noncardiovascular death, which to our knowledge has not been reported previously, and will have important clinical implications. Understanding these factors, as well as how the cardiovascular versus noncardiovascular mortality trends change over time, can play a role in informing prognosis in patients post-TAVI. Our data can therefore influence how a particular patient is managed long-term by both the heart team and primary care providers, particularly from a surveillance perspective. Future directions for this research would involve stratifying patients by surgical risk to determine if these groups have different predictors of long-term mortality.

Table 3
Fine-Gray model for cardiac and noncardiac mortality from April 2011 to December 2016

Parameter	Cardiac Mortality			Noncardiac Mortality		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Age	1.04	1.02−1.06	0.0003	1.02	1.00−1.04	0.02
Charlson score	1.12	1.01−1.23	0.03	1.10	1.00−1.21	0.05
Frailty score	1.02	1.00−1.04	0.08	1.05	1.02−1.07	0.0001
Female	1.09	0.86−1.39	0.47	0.70	0.55−0.89	0.0038
Rural residence	1.35	0.97−1.88	0.07	0.95	0.67−1.36	0.79
Transfemoral access	0.70	0.53−0.92	0.01	0.73	0.56−0.94	0.01
Urgent procedure	1.44	1.10−1.87	0.01	1.02	0.78−1.33	0.90
Hypertension	0.82	0.51−1.32	0.41	0.85	0.54−1.34	0.48
Diabetes	1.01	0.77−1.32	0.95	1.24	0.96−1.60	0.10
Congestive heart failure	1.52	1.09−2.11	0.01	1.13	0.85−1.50	0.41
COPD	1.08	0.86−1.36	0.51	1.29	1.04−1.61	0.02
Arrhythmia	1.26	1.00−1.59	0.05	1.18	0.93−1.50	0.18
Cancer	0.76	0.45−1.27	0.29	1.05	0.68−1.63	0.81
CAD/ischemic heart disease	0.92	0.68−1.24	0.59	1.19	0.91−1.57	0.21
Cerebrovascular disease	1.03	0.66−1.60	0.90	0.63	0.38−1.03	0.07
Peripheral vascular disease	1.19	0.79−1.77	0.40	1.32	0.90−1.96	0.16
Dementia	1.36	0.94−1.95	0.10	0.80	0.54−1.20	0.29
Dialysis	0.89	0.51−1.55	0.69	1.48	0.88−2.47	0.14
Dyslipidemia	0.98	0.77−1.26	0.90	1.01	0.80−1.27	0.96
Liver disease	0.75	0.23−2.43	0.63	1.36	0.58−3.15	0.48
Interstitial lung disease	1.46	0.77−2.77	0.24	1.12	0.59−2.13	0.72
Renal disease	0.94	0.64−1.38	0.75	0.69	0.46−1.04	0.08
Percutaneous coronary intervention	1.00	0.77−1.29	0.98	0.64	0.50−0.81	0.0003
Previous CABG	0.92	0.69−1.23	0.58	0.70	0.52−0.94	0.02
Previous valve surgery	1.08	0.78−1.48	0.65	0.81	0.57−1.15	0.24
Income quintile						
1	1.04	0.72−1.50	0.85	0.94	0.67−1.33	0.73
2	1.25	0.89−1.75	0.19	0.98	0.71−1.35	0.92
3	0.91	0.63−1.31	0.62	0.89	0.64−1.24	0.49
4	1.13	0.78−1.62	0.52	0.76	0.53−1.08	0.13
5 (reference)	1.00	N/A	N/A	1.00	N/A	N/A

CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease.

A number of limitations of our study merit discussion. Firstly, the surgical risk profiles of patients who underwent TAVI and transcatheter heart valve devices used in the procedure have changed significantly and may not be directly comparable over the study period. Secondly, the event rate for repeat intervention was very low, which lends itself to the possibility of type II statistical error for this outcome. Thirdly, we used reported cause of death based on death certificates, which may have inaccuracies. That said, we have used the same broad classification of cardiovascular versus noncardiovascular causes of death used by other previous studies. We did not have some follow-up echocardiography data, and as such cannot comment on structural valve deterioration. Finally, our study could not account for a number of confounders given its observational nature. For this reason, our conclusions should be considered hypothesis-generating rather than conclusive.

In conclusion, this study revealed that noncardiovascular death is the most common cause of death in the long term post-TAVI. There are unique predictors of cardiovascular versus noncardiovascular death suggesting different approaches to the short and long-term follow-up of these patients by the heart team and primary care providers.

Authors contribution

Mithunan Ravindran: Conceptualization, Writing - Original Draft. **Kayley A. Henning**: Conceptualization, Writing - Original Draft. **Feng Qiu**: Formal Analysis, Writing - Review & Editing. **Ragavie Manoragavan**: Writing - Review & Editing. **Danny Dvir**: Writing - Review & Editing. **Mony Shuvy**: Writing - Review & Editing. **Maneesh K. Sud**: Writing - Review & Editing. **Harindra C. Wijeysundera**: Conceptualization, Writing - Review & Editing, Supervision.

Disclosures

The authors have no conflicts of interest to disclose.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Table 4
Fine-Gray model for repeat TAVI/SAVR from April 2011 to December 2016

Parameter	Hazard Ratio	95% CI	p-value
Age	0.96	0.94−0.98	0.0003
Charlson score	1.07	0.90−1.27	0.44
Frailty score	1.00	0.96−1.05	0.97
Female	0.62	0.39−0.98	0.04
Rural residence	1.21	0.64−2.30	0.55
Transfemoral access	1.45	0.72−2.93	0.30
Urgent procedure	0.68	0.36−1.29	0.24
Hypertension	0.47	0.25−0.86	0.01
Diabetes	0.93	0.56−1.54	0.77
Congestive heart failure	0.75	0.46−1.21	0.24
COPD	1.09	0.69−1.73	0.71
Arrhythmia	0.68	0.39−1.20	0.18
Cancer	1.64	0.77−3.49	0.20
CAD/Ischemic heart disease	0.70	0.42−1.17	0.17
Cerebrovascular disease	0.75	0.22−2.54	0.65
Peripheral vascular disease	1.32	0.57−3.03	0.52
Dementia	1.21	0.50−2.95	0.67
Dialysis	1.52	0.50−4.59	0.46
Dyslipidemia	0.80	0.51−1.26	0.33
Liver disease	1.22	0.41−3.65	0.72
Interstitial lung disease	3.37	1.27−8.93	0.01
Renal disease	0.61	0.20−1.79	0.36
Percutaneous coronary intervention	1.13	0.68−1.88	0.65
Previous CABG	1.06	0.59−1.89	0.85
Previous valve surgery	1.68	0.96−2.95	0.07
Income quintile			
1	1.87	0.85−4.11	0.12
2	2.45	1.18−5.10	0.02
3	1.91	0.90−4.05	0.09
4	1.70	0.77−3.79	0.19
5 (reference)	1.00	N/A	N/A

CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.08.046.

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