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Impact of Transcatheter Aortic Valve Durability on Life Expectancy in Low-Risk Patients With Severe Aortic Stenosis

Derrick Y. Tam, MD, PhD
Harindra C. Wijeysundera, MD, PhD
David Naimark, MD, MSc
Mario Gaudino, MD
John G. Webb, MD
David J. Cohen, MD, MSc
Stephen E. Fremes, MD, MSc

BACKGROUND: Recent clinical trial results showed that transcatheter aortic valve replacement (TAVR) is noninferior and may be superior to surgical aortic valve replacement (SAVR) for mortality, stroke, and rehospitalization. However, the impact of transcatheter valve durability remains uncertain.

METHODS: Discrete event simulation was used to model hypothetical scenarios of TAVR versus SAVR durability in which TAVR failure times were varied to determine the impact of TAVR valve durability on life expectancy in a cohort of low-risk patients similar to those in recent trials. Discrete event simulation modeling was used to estimate the tradeoff between a less invasive procedure with unknown valve durability (TAVR) and that of a more invasive procedure with known durability (SAVR). Standardized differences were calculated, and a difference >0.10 was considered clinically significant. In the base-case analysis, patients with structural valve deterioration requiring reoperation were assumed to undergo a valve-in-valve TAVR procedure. A sensitivity analysis was conducted to determine the impact of TAVR valve durability on life expectancy in younger age groups (40, 50, and 60 years).

RESULTS: Our cohort consisted of patients with aortic stenosis at low surgical risk with a mean age of 73.4±5.9 years. In the base-case scenario, the standardized difference in life expectancy was <0.10 between TAVR and SAVR until transcatheter valve prosthesis failure time was 70% shorter than that of surgical prostheses. At a transcatheter valve failure time <30% compared with surgical valves, SAVR was the preferred option. In younger patients, life expectancy was reduced when TAVR durability was 30%, 40%, and 50% shorter than that of surgical valves in 40-, 50-, and 60-year-old patients, respectively.

CONCLUSIONS: According to our simulation models, the durability of TAVR valves must be 70% shorter than that of surgical valves to result in reduced life expectancy in patients with demographics similar to those of recent trials. However, in younger patients, this threshold for TAVR valve durability was substantially higher. These findings suggest that durability concerns should not influence the initial treatment decision concerning TAVR versus SAVR in older low-risk patients on the basis of current evidence supporting TAVR valve durability. However, in younger low-risk patients, valve durability must be weighed against other patient factors such as life expectancy.

Key Words: heart valves ■ prosthesis failure ■ structural valve deterioration

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Clinical Perspective

What Is New?

- Two recent randomized clinical trials in patients with severe aortic stenosis at low surgical risk showed improved 30-day outcomes and similar 1-year outcomes with transcatheter aortic valve replacement (TAVR) compared with surgical aortic valve replacement.
- However, concerns remain in the cardiovascular community about the expansion of TAVR to low-surgical-risk patients because of the uncertainty of TAVR valve durability in this population.

What Are the Clinical Implications?

- This study used decision analysis techniques, specifically discrete event simulation, to realistically model the durability of transcatheter valves compared with the known existing durability of surgical aortic biological prostheses over the lifetime of a low-risk patient.
- The durability of TAVR valves must be 70% shorter than that of surgical biological prostheses to have an impact on overall life expectancy in low-risk older patients with characteristics similar to those of patients in clinical trial undergoing TAVR.
- This study puts into context concerns about TAVR valve durability and suggests that, on the basis of current knowledge, durability concerns should not influence the initial treatment decision for TAVR versus surgical aortic valve replacement in patients similar to those in low-risk clinical trials (mean age, 73 years).

Transcatheter aortic valve replacement (TAVR) has rapidly evolved to become the standard of care for the treatment of aortic stenosis (AS), fueled by a robust evidence base of randomized, controlled trials comparing TAVR with surgical aortic valve replacement (SAVR) in patients at high and intermediate surgical risk[1,2] and most recently in patients at low surgical risk.[3,4] A key limitation in this evidence has been the limited follow-up and thus concerns about TAVR valve durability. This is particularly true in patients at low surgical risk whose mean age (73 years) was much lower than that in earlier trials of intermediate-risk patients (81 years) and patients at high surgical risk (83 years). Given this uncertainty, several editorials have called for publication of 10-year durability data before the performance of TAVR in low-risk patients.[5–7] Delaying access of TAVR in such patients until long-term data are available is unlikely to be informative, however, given the rapid rate of device iterations, which would make long-term data on current transcatheter heart prostheses obsolete in 10 years. Moreover, there is a substantial opportunity cost in restricting access of a beneficial intervention because of a hypothetical long-term concern.

Discrete event simulation (DES) is a decision analytic technique involving patient-level simulation that can model competing events and affords a method to quantify the tradeoffs between early benefit of an intervention (TAVR in this situation) and hypothetical long-term harms resulting from durability concerns.[8] Here, we use DES to model hypothetical scenarios of transcatheter heart prosthesis versus surgical biological prosthesis durability to estimate the impact of TAVR valve durability on life expectancy. In the absence of long-term follow-up from randomized clinical trials, this technique provides a quantitative projection of the potential consequences of poor TAVR valve durability on survival.

METHODS

This analysis was conducted using published data that can be found indexed in PubMed. References for all model inputs have been provided.

Overview

DES models simulate the life trajectory of individual hypothetical patients from a given starting point (eg, diagnosis or surgery) until an exit condition occurs: either death or survival beyond a fixed time horizon.[8] Between the starting point and exit, patients move from 1 event to another and thereby accumulate elapsed time and increased age. Unlike discrete time Markov (state transition) models, the time intervals between events in a DES model are generally variable and continuous. For example, an event that occurs 17.5 years after the starting point would require a hypothetical person to iterate through a Markov model, with fixed annual intervals, 18 times, whereas the same event can be represented as a single step with a time interval of 17.5 years in a DES model. Therefore, the DES structure allows much more computational efficiency than conventional Markov models.

For the current analysis, a DES model was constructed using a hypothetical patient population with characteristics similar to that of the PARTNER 3 trial (Placement of Aortic Transcatheter Valves), a recent randomized clinical trial that compared balloon-expandable TAVR with SAVR in patients at low surgical risk (Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score <4%) with severe AS. The mean age of our simulated patients was 73.3±5.8 years; 69.3% were male; and there were the typical proportions of cardiac comorbidities sampled from the distributions found in the PARTNER 3 trial. In the model, patients underwent an index procedure (TAVR or SAVR) and were at risk for perioperative mortality (0.4% and 1.1% for TAVR and SAVR, respectively); those who survived were then at risk for late events. Among the latter patients, a fixed time horizon of 40 years was specified, and each patient was assigned a random time for 2 other late events (reoperation or background mortality) derived from a probabilistic sampling from time-to-event distributions based on literature. Background mortality was obtained through age- and sex-specific 2017 US life tables, which were converted into corresponding age- and sex-specific Gompertz time-to-event distributions from which time to background mortality was sampled for each simulated

patient. Time to reoperation was obtained from a published meta-analysis of 13 studies involving 9007 bioprosthetic valves with a total of 54 151 patient-years of follow-up and used a Weibull time-to-event distribution.[9] There were 2 possible outcomes for every patient: background mortality and reoperation. For each patient, a time to death and a time to reoperation were generated. Subjects were followed up to the first of these 2 events or to the end of the model time horizon (whichever occurred first). If the shortest event time was either death or survival past the time horizon, the patient exited the model without a reoperation. On the other hand, if reoperation was the shortest event time, the patient underwent a reoperation and was at risk for reoperative mortality. Reoperative mortality was estimated with the STS-PROM calculator and incorporated the previous number of operations, age at the time of reoperation, baseline cardiac comorbidities, and new potential comorbidities at the time of reoperation (ie, status of operation, need for balloon pump, heart failure status, cardiogenic shock) according to characteristics from a previously published cohort of contemporary redo SAVR patients.[10,11] For patients who survived reoperation, a new event time for reoperation was sampled from the valve failure time-to-event distribution, the parameters of which were updated according to the patient's current age in the model, and time to the horizon was recalculated. Once again, the patient experienced the event with the shortest time to event. In this model, no more than 3 reoperations were possible, and patients were modeled to succumb if the fourth valve failed. The model progressed until all patients had either entered the death state or survived beyond a maximum time horizon of 40 years. This model was constructed in Treeage 2019 (Williamstown, MA). A schematic of the DES model is provided in Figure 1.

A detailed explanation of the model inputs and underlying assumptions is provided in Methods in the Data Supplement. Sensitivity analyses examining the impact of valve durability as a function of different biological porcine and pericardial valve types are also described in detail in Methods in the Data Supplement.

Statistical Analysis

In the base-case analysis, each simulated SAVR patient's life expectancy was based on the current sampled time to surgical valve prosthesis reoperation. The TAVR life expectancy for the same matched patient was estimated by applying an event-time ratio (ETR) from 0.1 to 1.0 to that patient's surgical prosthesis sampled time to reoperation. An ETR of 1.0 indicates identical time to reoperation between TAVR and SAVR; an ETR of 0.5 would yield a TAVR reoperation time half that of an SAVR valve for the exact same patient. The ETR can be viewed as an accelerated time to failure factor with ETR <1 indicating earlier valve failure. We felt that it was prudent not to limit the model and instead to examine the impact of the full range of ETR from 0.1 to 1.0 because studies have shown very early valve failures in surgical valves (ie, the Mitroflow biological prosthesis), which would be approximated by ETRs of 0.2 to 0.3.[12] We compared life expectancy in a model of 25 000 patients at each ETR. We chose a cohort of 25 000 hypothetical patients because model outputs were stable with this number of simulated patients. Standardized differences in the life expectancy between index TAVR and

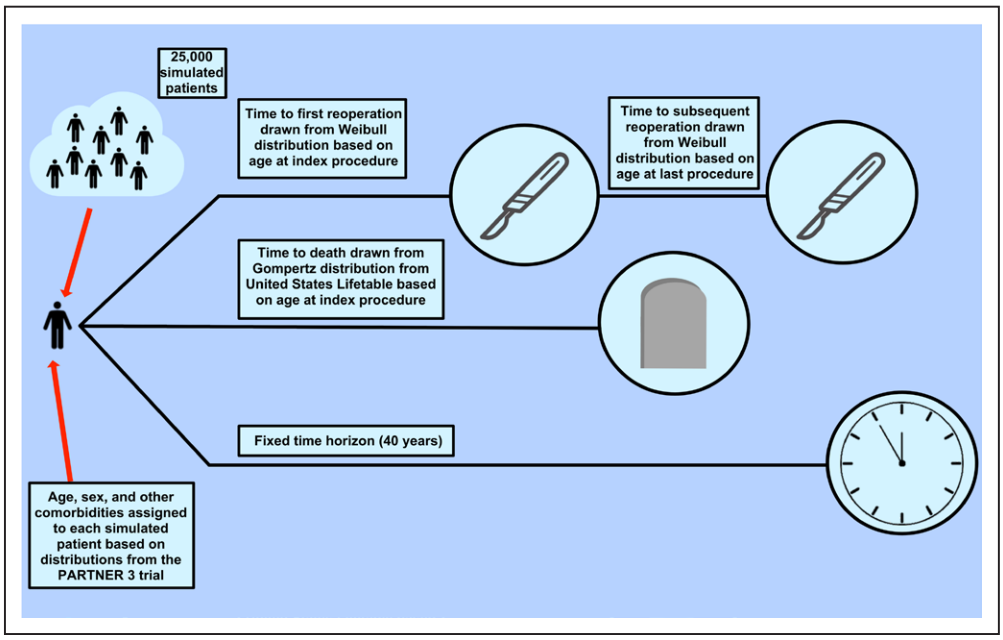

Figure 1. Schematic of discrete event simulation (DES) model potential pathway.
In this DES model, patients were assigned distinct baseline characteristics such as age, sex, and other cardiac comorbidities according to distributions from the PARTNER 3 trial (Placement of Aortic Transcatheter Valves). A patient who survives the index procedure was at risk for 2 competing events: reoperation and death. In a DES model, there is an explicit simulation clock such that time is continuous. Patients advance from 1 state to another at discrete intervals based on sampled time to events. The event with the shortest time takes place first. In this example, the patient would undergo reoperation first. The time to second reoperation would be resampled on the basis of the patient's age at the first reoperation. However, in this example, the patient would not undergo a second reoperation because the next event to take place would be death. The model terminates when the patient dies or after 40 years have elapsed (the time horizon and prespecified stop point of the model). This process is repeated for all 25 000 simulated patients, first in the transcatheter aortic valve replacement arm and then again in the surgical aortic valve replacement arm. The time spent alive in each iteration of the model is recorded as life expectancy and then averaged at the end of 25 000 simulations.

Table 1. Baseline Characteristics From the Model and Characteristics at the Time of Reoperation

	SAVR	TAVR
n	25 000	25 000
Age, mean (SD), y	73.3 (5.8)	73.3 (5.8)
Male, n (%)	17 427 (69.7)	17 427 (69.7)
Congestive heart failure, n (%)	6940 (27.8)	6940 (27.8)
Diabetes mellitus, n (%)	7762 (31.0)	7762 (31.0)
Hypertension, n (%)	20 058 (80.2)	20 058 (80.2)
Atrial fibrillation, n (%)	4287 (17.1)	4287 (17.1)
Chronic lung disease, n (%)	1535 (6.1)	1535 (6.1)
Peripheral vascular disease, n (%)	1737 (6.9)	1737 (6.9)
Dialysis,* n (%)	954 (3.8)	954 (3.8)
IABP use,* n (%)	131 (0.5)	131 (0.5)
Cardiogenic shock,* n (%)	488 (2.0)	488 (2.0)
Urgent status at reoperation,* n (%)	9452 (37.8)	9452 (37.8)
Emergent status at reoperation,* n (%)	612 (2.4)	612 (2.4)
STS score at first reoperation, n (%)	3.2 (2.2)	3.2 (2.2)

IABP indicates intra-aortic balloon pump; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

*Variables at the time of reoperation and entered into the STS score to predict mortality at reoperations.

SAVR were calculated at each ETR to determine which treatment strategy yielded longer or similar life expectancy. Standardized differences are independent of sample size and were calculated by taking the difference of the mean and dividing by the mean SD.[13] This calculation is also known as the Cohen *d* and is a measure of effect size that is not influenced by sample size. Although cutoffs for what is considered a significant effect size may vary by outcome and study, we considered a difference of 0.10 to be clinically important. This is the same cutoff used in biomedical studies to denote acceptable balance in propensity score–matched cohorts.[14] The base-case analysis used the following sequence of reoperative strategies for a failed index procedure: index procedure (SAVR or TAVR)→first reoperation: TAVR in SAVR (for index SAVR) or TAVR in TAVR (for index TAVR)→second reoperation: TAVR in TAVR→third reoperation: redo SAVR→fourth reoperation: death.

On the basis of a previous meta-analysis comparing valve-in-valve TAVR to redo SAVR, observed to expected mortality was ≈23% lower with valve-in-valve TAVR.[13] Thus, in this analysis, the individual's STS-PROM score was reduced by 23% in all patients undergoing valve-in-valve TAVR and equal to the STS-PROM score in those undergoing redo SAVR. A maximum of 4 total procedures were allowed before the patient succumbed.

Scenario Analysis

We considered a scenario in which reoperation for a late failed TAVR valve was a higher-risk redo operation (ie, TAVR explantation and SAVR) and the relative risk of reoperation was increased by 2-fold compared with those in the SAVR arm. Similar to the base case, ETR was varied from 0.1 to 1.0 in increments of 0.1, and each simulation included 25 000 patients per arm. Life expectancy was compared between the treatment arms at each ETR. Finally, we examined the impact of age at the index procedure (40, 50, 60, 70, and 80 years) on life expectancy in the base-case analysis at ETRs from 0.1 to 1.0 in increments of 0.1. In this sensitivity analysis, only the age of the patient, which in turn influenced background mortality, time to reoperation, and reoperative mortality, was changed.

Institutional review board approval was not necessary given that this analysis was conducted with published data sets.

RESULTS

Baseline characteristics were identical between the treatment strategies because the same patient entered each arm of simulation and thus served as his or her own internal control. The overall population was 69.7% male with a mean age of 73.3±5.8 years (Table 1). The estimated STS-PROM score for the first reintervention was 3.2±2.2%.

In the base-case analysis, if SAVR durability and TAVR durability were the same (ie, ETR=1.0), similar life expectancies between the 2 treatment arms were observed, although life expectancy was numerically higher for TAVR than SAVR (13.7 years for SAVR versus 13.9 years for TAVR; standardized difference, 0.015; Figure 2). The point estimate for TAVR was the same or greater than SAVR for all ETRs >0.6. Below 0.6, the point estimates for SAVR life expectancy were greater, and only when the ETR was <0.3 was the standardized difference >0.10. In other words, only when TAVR durability was worse than 70% of that of a surgical prosthesis was there a clinically important difference in life expectancy between the 2 arms. To help contextualize the clinical significance of the ETR, for an individual of 74 years of age (mean age of the trial patients), the median time to reoperation was 18 years when the ETR was 1.0 and 5.4 years when the ETR was 0.3. The relationship between ETR and the median estimated time to reoperation for the base analysis and different age groups is provided in Table 2. In the base-case analysis, for a PARTNER 3–like cohort in which the mean age was 73.3±5.8 years, the expected life expectancy for this cohort was 13 years (interquartile range, 8–20). The need for at least 1 reoperation when the ETR was 1.0 was 33% and similar between TAVR and SAVR (Figure 3). Fewer than 3% of patients required a second reoperation in their lifetime when the ETR was 1.0. When the ETR was 0.3, 81%, 56%, and 31% of patients with TAVR required 1, 2, and 3 reoperations, respectively. When the ETR was 1.0, 1.0% of total patients died as a result of reoperation, whereas 13.2% of patients died as a result of reoperation when the ETR was 0.3.

In the scenario analysis in which reoperation for TAVR was considered high risk and reoperative mortality was double the predicted STS-PROM score, there

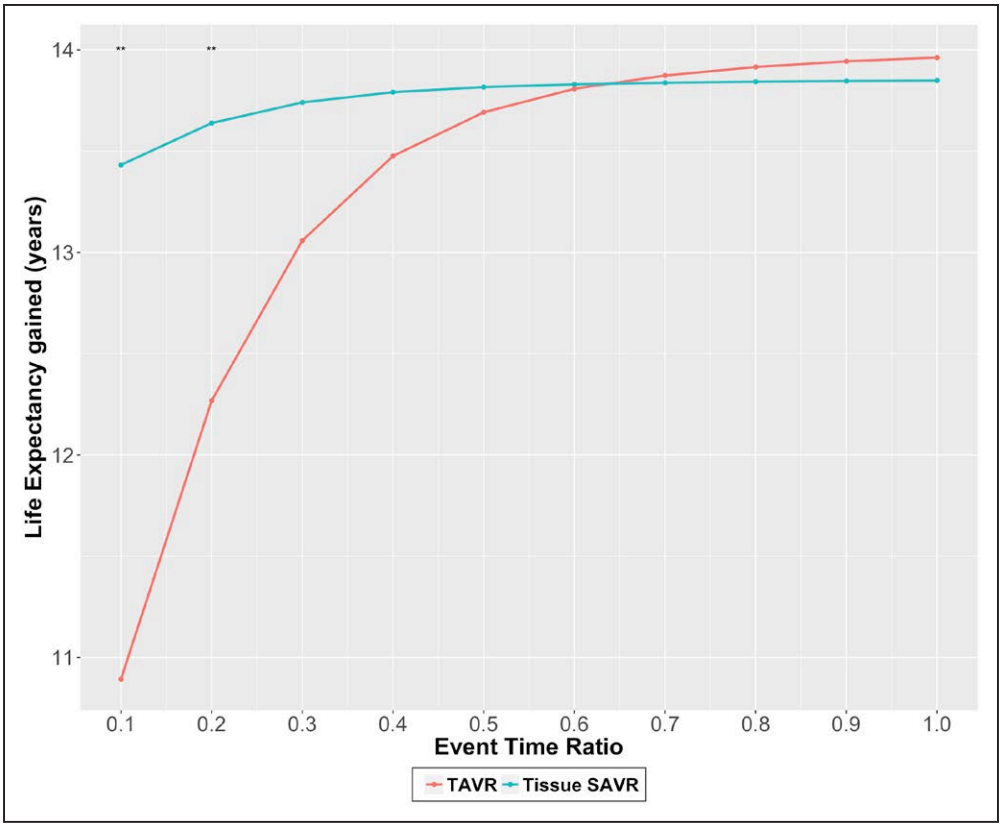

Figure 2. Results of base-case analysis.
Results of the base case examining the impact of the event time ratio (ETR) for transcatheter aortic valve replacement (TAVR) valve durability on life expectancy when patients undergo valve-in-valve TAVR as the initial management strategy for a failed prosthesis. An ETR of 1 denotes TAVR durability similar to that of a surgical biological prosthesis; an ETR of 0.1 denotes a valve failure time that is 1/10th that of a surgical biological prosthesis. Standardized differences in life expectancy were calculated between the 2 treatment arms, and a standardized difference of 0.10 was considered clinically important. Life expectancy was similar between TAVR and surgical aortic valve replacement (SAVR) until an ETR of <0.3. When the ETR was <0.3, the gain in life expectancy was higher with an index SAVR strategy.

was no clinically meaningful difference in life expectancy between TAVR and SAVR when the ETR was ≥0.3 (Figure 4). When the ETR was <0.3, SAVR was the preferred index treatment of choice. In our analysis examining the relationship between age of index procedure and the ETR threshold, there was a clear inverse relationship with age. For the index procedures ages of 40, 50, 60, 70, and 80 years, standardized differences were >0.10 (favoring SAVR) when the ETRs were <0.7, 0.6, 0.5, 0.4, and 0.3, respectively (Figure 5 and Figures I–V in the Data Supplement).

DISCUSSION

Guidelines for the management of AS in low-risk patients are likely to evolve given the recent findings from both the PARTNER 3 trial and the CoreValve Low Risk trial with caveats for the unknown durability of TAVR valves. This DES model provides support for the use of TAVR in low-risk patients similar to the PARTNER 3 cohort. In essence, TAVR valves need to be only 30% as durable as currently used surgical biological prostheses to achieve similar life expectancies with SAVR. The implications for current clinical decision making in AS is critical; specifically, for SAVR to be the preferred initial therapeutic option as a result of concerns about durability alone, TAVR valve durability must be 70% shorter than that of surgical bioprostheses. To contextualize these findings in a PARTNER 3–like cohort, in whom the average life expectancy in the United States is 13 years for a 73-year-old, only when TAVR valves fail within 4 to 6 years after the index surgery would we see an impact on life expectancy because of the need for at least 1 reoperation in an estimated 80% of these patients. Although we show the risks associated with the first reoperation to be low, particularly if valve-in-TAVR is performed, the decrement in life expectancy is realized when the majority of patients require ≥1 reinterventions rather than the minority when durability is similar to that of surgical valves.

This is an important insight; current evidence suggests that transcatheter prosthesis will likely surpass the benchmark described above. In the NOTION all-comers trial (Nordic Aortic Valve Intervention), in which the mean age of patients was 79 years, there was no difference at the 6-year follow-up for bioprosthetic valve failure (defined as valve-related death, aortic valve reintervention, or severe structural valve

Table 2. ETRs and the Median Estimated Time to Valve Reoperation for Various Age Groups and the Base-Case Analysis

	Median Estimated Time to Valve Reoperation, y					
ETR	40	50	60	70	80	Base Case (Mean Age, 74 y)
1.0	12.3 (9.8-14.8)	13.8 (10.9–16.6)	15.5 (12.3–18.6)	17.4 (13.8–20.9)	19.5 (15.5–23.4)	18 (14.3–21.8)
0.9	11.1 (8.8–13.3)	12.4 (9.9–14.9)	14 (11.1–16.8)	15.7 (12.4–18.8)	17.6 (13.9–21.1)	16.2 (12.8–19.6)
0.8	9.9 (7.8–11.8)	11.1 (8.8–13.3)	12.4 (9.8–14.9)	13.9 (11–16.7)	15.6 (12.4–18.7)	14.4 (11.4–17.5)
0.7	8.6 (6.8–10.4)	9.7 (7.7–11.6)	10.9 (8.6–13)	12.2 (9.6–14.6)	13.7 (10.8–16.4)	12.6 (10–15.3)
0.6	7.4 (5.9–8.9)	8.3 (6.6–10)	9.3 (7.4–11.2)	10.4 (8.3–12.5)	11.7 (9.3–14.1)	10.8 (8.6–13.1)
0.5	6.2 (4.9–7.4)	6.9 (5.5–8.3)	7.8 (6.1–9.3)	8.7 (6.9–10.4)	9.8 (7.7–11.7)	9 (7.1–10.9)
0.4	4.9 (3.9–5.9)	5.5 (4.4–6.6)	6.2 (4.9–7.4)	7 (5.5–8.4)	7.8 (6.2–9.4)	7.2 (5.7–8.7)
0.3	3.7 (2.9–4.4)	4.1 (3.3–5)	4.7 (3.7–5.6)	5.2 (4.1–6.3)	5.9 (4.6–7)	5.4 (4.3–6.5)
0.2	2.5 (2–3)	2.8 (2.2–3.3)	3.1 (2.5–3.7)	3.5 (2.8–4.2)	3.9 (3.1–4.7)	3.6 (2.9–4.4)
0.1	1.2 (1–1.5)	1.4 (1.1–1.7)	1.6 (1.2–1.9)	1.7 (1.4–2.1)	2 (1.5–2.3)	1.8 (1.4–2.2)

ETR indicates event-time ratio. The projected life expectancy in the United States (2017) for 40-, 50-, 60-, 70-, 80- year-old individuals (both sexes) is 40.7, 31.6, 23.3, 15.7, and 9.2 years, respectively. Note that the longer time to reoperation seen in the model for the oldest age group may be a reflection of the reluctance to reoperate on frail and elderly patients with structural valve deterioration in older studies of valve durability and thus should be interpreted with caution.

deterioration [SVD] by gradients) between TAVR and SAVR (7.5% versus 6.7%; *P*=0.89).[15] In the UK TAVI registry (Transcatheter Aortic Valve Implantation), 241 patients were followed up for a median of 5.8 years. Only 1 patient demonstrated severe SVD at the 5-year follow-up, and 90.9% of patients were free from any SVD in this study.[16] Nonetheless, the patients in these follow-up studies were older than the PARTNER 3 patient population. Given that surgical valve durability is a function of both the patient's age at the time of implantation and the time since implantation, our analysis compared relative valve durability using the ETR and thus offers insight into SVD in the low-risk patient population. In our sensitivity analysis, we found that TAVR valve durability was of greater importance in younger patients. Indeed, at a TAVR valve durability 30% to 40% worse than that of surgical valves, life expectancy was reduced in 40- and 50-year-old patients, respectively. This reinforces the notion that current evidence is applicable to patients with AS who are low risk but nonetheless elderly (mean age, ≈73 years) and suggests that, in young low-risk patients, SAVR may be the treatment of choice if durability is a concerning factor.

Transcatheter valve technology has also revolutionized the management of failed biological prosthetic valves. Evidence from a recent meta-analysis suggests that although early mortality was similar between valve-in-valve TAVR and redo SAVR, the expected mortality in the TAVR group was higher and thus risk-adjusted mortality is likely lower with TAVR.[17] In our analysis, the ETR threshold for equivalent life expectancy was similar in patients who could undergo valve-in-valve TAVR or high-risk redo SAVR. It is important to note that not all patients are eligible for valve-in-valve TAVR in the presence of specific anatomic factors or previous valve size factors that would preclude a valve-in-valve procedure. However, novel advances in biological prosthesis fracturing at the time of the valve-in-valve procedure may facilitate the placement of larger TAVR valves.[18,19] In addition, concerns about coronary obstruction from the previous bioprosthesis may potentially be managed by the bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction (BASILICA) procedure in which the leaflets in the coronary sinuses are divided before valve-in-valve TAVR.[20] Although these techniques have increased the number of patients who can be treated with valve-in-valve TAVR, they are complex, require additional expertise, and may not be offered at every institution.

However, there is less evidence surrounding the management of late TAVR valve failure. TAVR-in-TAVR appears to be safe; in an international multicenter study of 14 centers from North America and Europe, a small sample of patients underwent TAVR-in-TAVR with zero mortality or stroke.[21] Less is known about outcomes after TAVR SVD requiring explantation and SAVR. In a review of the literature by Mylotte and colleagues,[22] the majority of patients underwent TAVR-in-TAVR, and the minority underwent SAVR; again, no deaths were observed in either group. In our scenario analysis in which reoperative mortality was double that of the STS-PROM score, findings were fairly robust in that survival was significantly reduced only when the durability of TAVR valves was 70% worse than that of surgical bioprostheses, which was similar to our base-case analysis. These findings from our model highlight 2 important points: Reoperation is uncommon in older patients because the valves tend to outlive the patient, and as a result, even in the face of higher reoperative mortality, the overall impact on the average life expectancy of a cohort of PARTNER 3–like patients is minimal.

A key variable in our analysis is time to valve failure and SVD, and thus, it is important to acknowledge that the concept of SVD and the definition of bioprosthetic valve failure are evolving in the literature.[23] Although

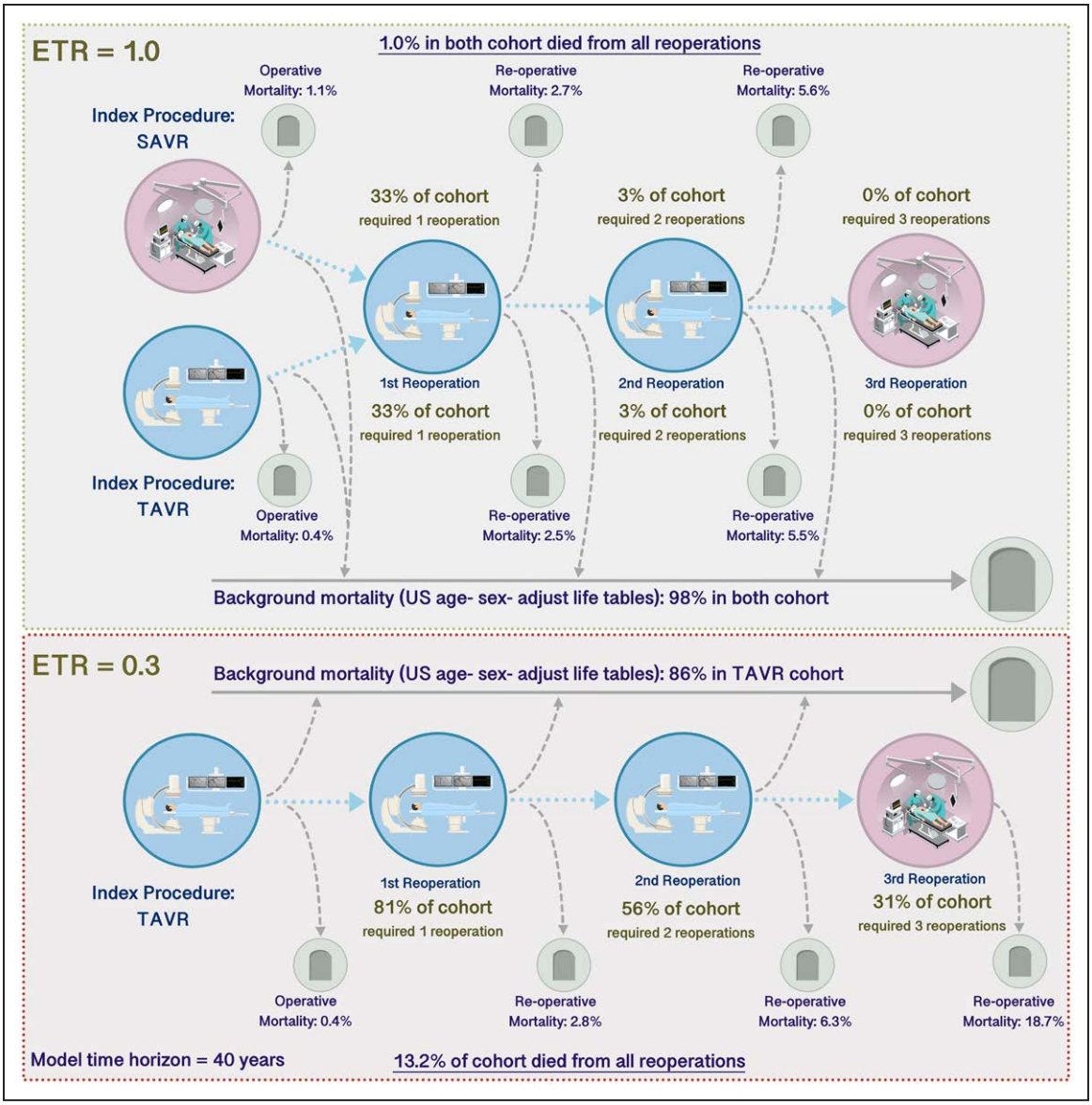

Figure 3. Summary of base-case model key outputs.
Summary of base-case model key outputs for an index treatment strategy of either surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) when the event-time ratio (ETR) was 1.0 and for TAVR when the ETR was 0.3. When the ETR was 1.0, 33% of the cohort required 1 reoperation and 3% of the cohorts require 2 reoperations. No patients in either cohort required a third reoperation. Ninety-eight percent of patients died as a result of background mortality, and <0.1% survived beyond the model time horizon and exited the model (not shown). When the ETR was 0.3, 81%, 56%, and 31% of patients with TAVR required 1, 2, and 3 reoperations, respectively. Of the patients with TAVR, 13.2% died of reoperation. Eighty-six percent of patients died as a result of background mortality, and 0% of patients survived beyond the model time horizon. In the base-case analysis, the first 2 reinterventions were SAVR-in-TAVR or TAVR-in-TAVR; the third reintervention was redo SAVR.

more than a dozen studies have examined surgical bioprosthesis durability beyond 10 to 20 years, the number of studies examining durability in transcatheter valves is much more limited, and few studies have a follow-up >5 years. Despite the plethora of studies that examined surgical valve durability, there remain limitations to the published literature on surgical valve durability that may be inherently biased. Early studies that included >20 years of patient follow-up often defined SVD as either death from valve failure or need for reoperation; therefore, these studies neglected other important outcomes such as valve failure leading to untreated heart failure. Although these are clinically important end points, systematic echocardiographic follow-up was lacking in these early studies; thus, these studies may have underestimated the true incidence of SVD, particularly in very elderly or frail patients in whom surgeons may have been reluctant to reoperate. Therefore, the longer time to reoperation seen in several studies for patients in the oldest age groups must be interpreted with caution.[24,25] In the era of TAVR, multiple societies have endeavored to change the definition of SVD to include increases in valve gradients in addition to need for reintervention.[26,27] Furthermore, the advent of valve-in-valve TAVR has allowed a larger pool

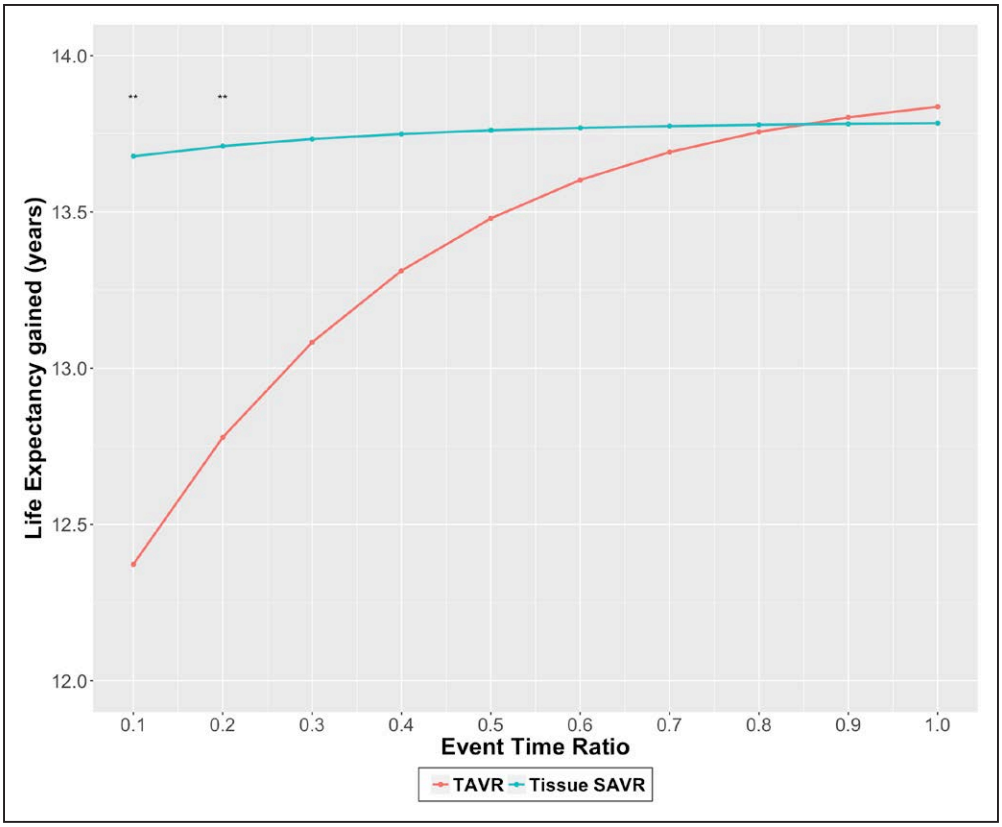

Figure 4. Results of scenario analysis of high reoperative risk.
Results of scenario analysis examining the impact of event-time ratio (ETR) for transcatheter aortic valve replacement (TAVR) valve durability on life expectancy in the setting of very high reoperative mortality for all patients. An ETR of 1 denotes TAVR durability similar to that of a surgical biological prosthesis; an ETR of 0.1 denotes a valve failure time that is 1/10th that of a surgical biological prosthesis. Standardized differences in life expectancy were calculated between the 2 treatment arms, and a standardized difference of 0.10 was considered significant. When the ETR was <0.3, the gain in life expectancy was higher with an index surgical aortic valve replacement (SAVR) strategy.

of patients to be treated for bioprosthetic valve failure, including those who are higher risk and more elderly.[28] Thus, the interpretation of our findings must be made in the context of what is known about surgical valve durability in the literature and the potential bias in time-to-reoperation data in the very elderly population.

Since the publication of the recent low-risk TAVR trials, the cardiovascular community has been divided on the role of TAVR in low-risk patients. Several editorials have called for additional data and 10-year follow-up before the adoption of TAVR for low-risk patients.[5–7] The objective of this simulation modeling was not to determine the optimal index treatment for the low-surgical-risk patient but rather to help inform clinical decision making, and this modeling suggests that the uncertainty in valve durability data should not influence the initial therapeutic decision in low-risk patients, at least under a broad range of plausible scenarios. There may be a tremendous opportunity cost to waiting for additional data before the adoption of this technology for low-risk patients; moreover, once 10-year follow-up is available, these long-term data may no longer be applicable to the contemporary prostheses given rapid device iteration. Given these challenges, the use of decision analysis to project both known short-term and long-term hypothetical risks and benefits is important in clinical decision making. This analysis provides critical insights for clinicians to confidently recommend TAVR to the appropriate patient groups and to allow them to advise patients on the risks and benefits of TAVR versus surgery. Although both TAVR and SAVR may be reasonable, the heart team remains paramount in helping to personalize and optimize therapy for low-risk patients with AS using patient characteristics and anatomic factors.

Limitations

This analysis must be interpreted in the context of important limitations. This analysis assumes that after perioperative mortality from the index procedure, 2 sources of mortality exist: that related to the age- and sex-matched general population and reoperative mortality. We acknowledge that, although earlier studies suggest that older patients with aortic valve replacement (65–80 years of age) have a life expectancy similar to that of the general population,[29] a more recent study suggests that observed survival is worse compared with the general population regardless of age but the worse survival is most pronounced in younger patients (<50 years) compared with older patients (70–79 and >80 years).[30] In our analysis,

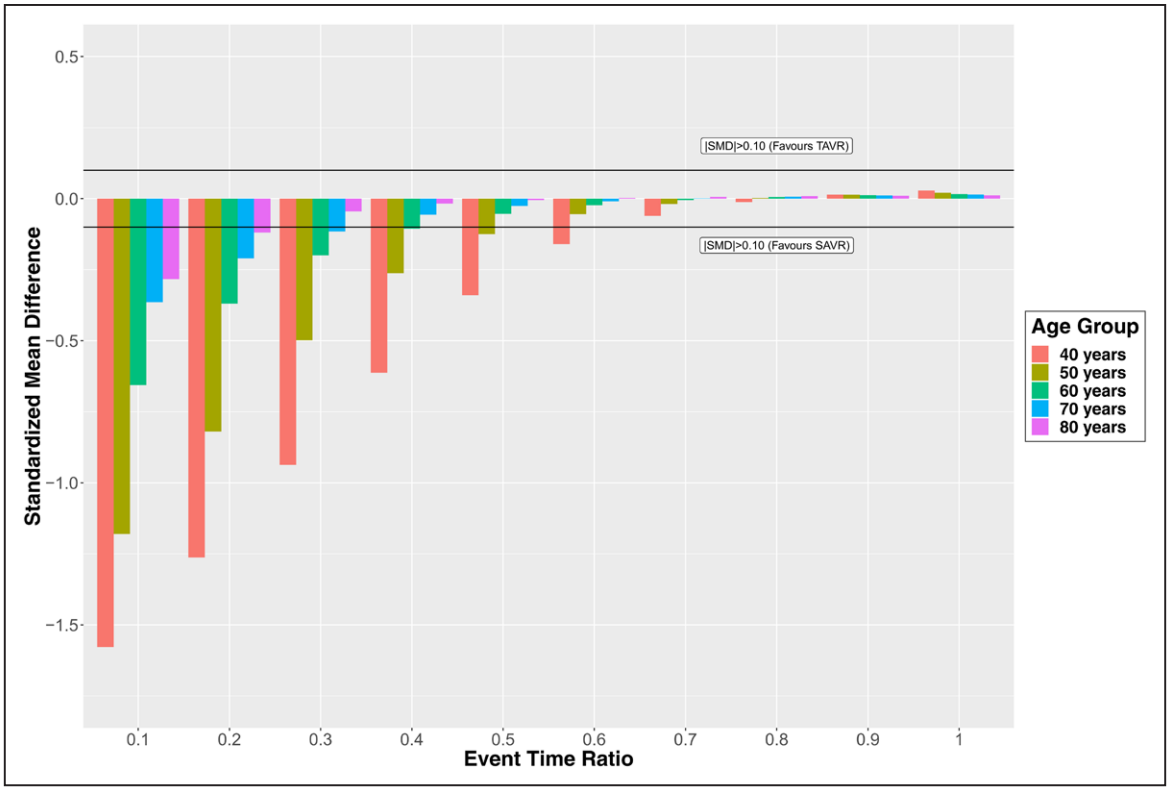

Figure 5. Relationship between age at index procedure and transcatheter aortic valve replacement (TAVR) durability.
The relationship between the age of the patient at index procedure and the standardized mean difference (SMD) at each event time ratio (ETR). An ETR of 1 denotes TAVR durability similar to that of a surgical biological prosthesis; an ETR of 0.1 denotes a valve failure time that is 1/10th that of a surgical biological prosthesis. The 2 horizontal lines denote an absolute SMD >0.10 (the cutoff for clinical significance in life expectancy used in this analysis). In older patients, the SMD was >0.10 when ETR thresholds were very low. On the contrary, in younger patients, the SMD was >0.10 event at intermediate ranges of ETR thresholds. Graphs for each of the 5 age groups comparing the life expectancy of TAVR and surgical aortic valve replacement strategies at each of the ETRs are found in Figures I through V in the Data Supplement.

we assumed that life expectancy is similar to that of the general population after aortic valve replacement, potentially systematically overestimating life expectancy in the model. This is a conservative assumption that biases to the null because it would favor SAVR given that TAVR durability is of greater concern with longer life expectancy. Furthermore, this model does not account for nonfatal complications (ie, stroke) or quality of life related to the actual procedure or procedural complications. Our model relied on early mortality outcomes from the PARTNER 3 randomized clinical trial, making use of a balloon-expandable transcatheter prosthesis via a transfemoral approach only. Therefore, outcomes may not be generalizable outside of the clinical trial setting or to other transcatheter prostheses and alternative access approaches. That said, recent observational evidence also suggests noninferior early outcomes between TAVR and SAVR in low-risk patients.[31] Nonetheless, we recognize that there were strict inclusion/exclusion criteria for TAVR in the low-risk populations; those with bicuspid valve disease, concomitant aortopathy, and severe aortic insufficiency were excluded in trial settings, although off-label use in these patients may be considered in the real-world setting. Unlike early TAVR trials, in PARTNER 3, the rate of moderate or greater paravalvular leak was similar between TAVR and SAVR, although the rate of mild paravalvular leak remained significantly higher with TAVR. We acknowledge that uncertainty remains concerning the impact of even mild paravalvular leaks on late mortality, although the data presented at Transcatheter Cardiovascular Therapeutics 2019 (San Francisco, CA)[31a] from the PARTNER 2A trial suggest a signal toward increased mortality associated with even mild paravalvular regurgitation (*P*=0.07). We used a Weibull distribution from a previously published meta-analysis to model time to reoperation from SVD; this meant that other causes for reoperation were not included in our model. Furthermore, although this meta-analysis included studies with extensive follow-up data, these data may not reflect the durability of contemporary valves. Although valve thrombosis is not uncommon after TAVR, the majority of cases are subclinical and clinical thrombosis that typically resolve with therapeutic anticoagulation.[32] We discuss the assumptions and limitations of using these data in additional detail in the Appendix in the Data Supplement. Although there are several possibilities for reoperation for failed valves, our analysis focused on 2 main strategies: reoperation with valve-in-valve TAVR and a potentially more complicated and high-risk redo SAVR in

patients with TAVR. We acknowledge that this model may be a simplification of a complex decision-making process. Although our DES model focused on outcomes of differences in life expectancy and overall survival for the population of interest, it may not capture a patient's preference for a less invasive strategy. Finally, our model included only biological prostheses in the surgical treatment arm, consistent with the design of the PARTNER 3 trial, and we acknowledge that this model was not designed to address the option of mechanical prostheses. Although the use of mechanical prostheses reduces concerns about valve durability, it raises other concerns about thromboembolism and bleeding and thus has become a less popular option, particularly in younger patients.[33]

Conclusions

The durability of TAVR valves must be 70% worse than that of surgical biological prostheses to have an impact on overall life expectancy in patients undergoing TAVR. This study puts into context concerns about TAVR valve durability and suggests that, on the basis of current knowledge, durability concerns should not influence the initial treatment decision for TAVR versus SAVR in older low-risk patients similar to those in the recent clinical trials. However, in younger low-risk patients, valve durability must be weighed against other patient factors such as life expectancy.

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Correspondence

Stephen E. Fremes, MD, MSc, Dr Bernard S. Goldman Chair in Cardiovascular Surgery, Schulich Heart Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room H4 05, Toronto, ON M4N 3M5, Canada. Email Stephen.fremes@sunnybrook.ca

Affiliations

Division of Cardiac Surgery, Departments of Surgery (D.Y.T., S.E.F.) and Medicine (H.C.W.), Schulich Heart Centre, Sunnybrook Health Sciences Centre, and Institute of Health Policy, Management and Evaluation (D.Y.T., H.C.W., D.N., S.E.F.), University of Toronto, ON, Canada. ICES, Toronto, ON, Canada (H.C.W.). Department of Cardiothoracic Surgery, Weill Cornell Medical College, New York (M.G.). Center for Heart Valve Innovation, St. Paul's Hospital, University of British Columbia, Vancouver, Canada (J.G.W.). Kansas City, MO (D.J.C.).

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Supplemental Materials

Expanded Methods–Model Inputs
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