Health Quality Ontario
The provincial advisor on the quality of health care in Ontario

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Transcatheter Aortic Valve Implantation for Treatment of Aortic Valve Stenosis: A Health Technology Assessment

KEY MESSAGES

The aortic valve is one of four valves in the heart. It allows blood to flow from the left ventricle of the heart into the aorta (the main artery in the body). Aortic valve stenosis occurs if the valve narrows and cannot open all the way, partially blocking the flow of blood out of the heart. Severe aortic valve stenosis can lead to death, usually from heart failure.

The diseased aortic valve can be removed and replaced with an artificial valve, but doing this involves open-heart surgery. Transcatheter aortic valve implantation, or TAVI, is a newer procedure. In most cases, cardiologists make a small opening in an artery near the groin to insert a catheter to deliver and implant the new valve.

We reviewed the research that compared TAVI with surgical aortic valve replacement. TAVI and surgery had similar rates of death, and both improved patients' quality of life in the first year. TAVI was associated with higher risk of stroke, major vascular complications, leakage of blood around the valve (aortic regurgitation), and the need for a pacemaker. Surgical aortic valve replacement was associated with a higher risk of bleeding. Another treatment option for people who cannot have surgical valve replacement involves using a balloon to open the blocked valve. People who had TAVI lived longer than people who had the balloon procedure. We also reviewed the economic evidence and developed an economic model to explore the cost-effectiveness of TAVI. We found that TAVI provided reasonably good value for money when compared with surgical aortic valve replacement.

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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ABSTRACT

Background

Surgical aortic valve replacement (SAVR) is the gold standard for treating aortic valve stenosis. It is a major operation that requires sternotomy and the use of a heart-lung bypass machine, but in appropriately selected patients with symptomatic, severe aortic valve stenosis, the benefits of SAVR usually outweigh the harms. Transcatheter aortic valve implantation (TAVI) is a less invasive procedure that allows an artificial valve to be implanted over the poorly functioning valve.

Methods

We identified and analyzed randomized controlled trials that evaluated the effectiveness and safety of TAVI compared with SAVR or balloon aortic valvuloplasty and were published before September 2015. The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

We also developed a Markov decision-analytic model to assess the cost-effectiveness of TAVI compared with SAVR over a 5-year time horizon, and we conducted a 5-year budget impact analysis.

Results

Rates of cardiovascular and all-cause mortality were similar for the TAVI and SAVR groups in all studies except one, which reported significantly lower all-cause mortality in the TAVI group and a higher rate of stroke in the SAVR group. Trials of high-risk patients who were not suitable candidates for SAVR showed significantly better survival with TAVI than with balloon aortic valvuloplasty. Median survival in the TAVI group was 31 months, compared with 11.7 months in the balloon aortic valvuloplasty group.

Compared with SAVR, TAVI was associated with a significantly higher risk of stroke, major vascular complications, paravalvular aortic regurgitation, and the need for a permanent pacemaker. SAVR was associated with a higher risk of bleeding. Transapical TAVI was associated with higher rates of mortality and stroke than transfemoral TAVI in high-risk patients. TAVI and SAVR both improved patients' quality of life during the first year. However, because of a large amount of missing data and the lack of published data beyond 1 year, it was difficult to evaluate the impact of critical adverse outcomes on patients' longer-term health status.

In the base-case analysis, when TAVI was compared with SAVR, the incremental cost-effectiveness ratio was $51,988 per quality-adjusted life-year. The 5-year budget impact of funding TAVI ranged from $7.6 to $8.3 million per year.

Conclusions

Moderate quality evidence showed that TAVI and SAVR had similar mortality rates in patients who were eligible for surgery. Information about quality of life showed similar results for TAVI and SAVR in the first year, but was based on low quality evidence. Moderate quality evidence also showed that TAVI was associated with higher rates of adverse events than SAVR. In patients who were not suitable candidates for surgery, moderate quality evidence showed that TAVI improved survival compared with balloon aortic valvuloplasty. When TAVI was compared with SAVR, the incremental cost-effectiveness ratio was $51,988 per quality-adjusted life-year.

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BACKGROUND

Health Condition

Aortic valve stenosis is a potentially serious condition that affects heart function by partially obstructing the blood flow from the heart to the aorta. It is usually caused by degenerative calcification (thickening of the valve leaflets and deposits of calcium that form nodules) or rheumatic fever. The degenerative form is most common in patients older than 65 years of age.

The aorta is the main artery in the body. It originates directly from the heart and supplies blood to all parts of the body. The aortic valve is a one-way valve located between the aorta and the left ventricle of the heart. Normally, the aortic valve has three small flaps, or leaflets, that open to allow blood to flow out of the heart and then close to prevent blood from flowing backwards into the heart again.

In healthy people, the aortic valve allows the unobstructed and one-way flow of blood, but if the aortic valve becomes diseased, two major conditions can occur: aortic valve stenosis and aortic valve insufficiency (leading to aortic regurgitation). Aortic valve stenosis occurs if the valve narrows and cannot open all the way, partially blocking blood flow out of the heart. Aortic insufficiency occurs when the valve cannot close completely and blood that has been pumped out of the heart leaks back into the left ventricle. In both conditions, the heart has to compensate and gradually becomes less able to supply enough blood and oxygen to the body, leading to heart failure. People who are born with abnormalities in the aortic leaflets, such as bicuspid aortic valve (two leaflets instead of three), are at higher risk of developing aortic valve stenosis. Such deformities may not cause problems until adulthood, at which time the valve may begin to show symptoms.

People with severe aortic valve stenosis experience chest pain, shortness of breath, and fatigue, making it difficult for them to go about the normal activities of daily living and reducing their quality of life. Severe aortic valve stenosis is also life-threatening: without surgery to replace the diseased aortic valve, people with symptoms of heart failure survive an average of less than 2 years.[1]

A recent study[2] has estimated the prevalence of aortic valve stenosis in people aged 75 years and older by conducting a systematic review and meta-analysis of population-based studies. The review included data from seven studies in six countries (USA, Switzerland, Belgium, Finland, Taiwan, the Netherlands). The pooled prevalence of all aortic valve stenosis was 12.4% (95% confidence interval [CI], 6.6%–18.2%), and the prevalence of severe aortic valve stenosis was 3.4% (95% CI, 1.1%–5.7%). Among those with severe aortic valve stenosis, 75.6% (95% CI, 65.8%–85.4%) were symptomatic. According to the original thresholds set by the Society for Thoracic Surgeons for risk of death from surgery, 5.2% of all elderly patients who underwent SAVR were considered high-risk (≥ 10% risk of death), 15.8% were intermediate-risk (5% to 9.9% risk of death), and 79.1% were low-risk (< 5% risk of death).

Clinical Need and Target Population

Surgical Aortic Valve Replacement

Surgical aortic valve replacement (SAVR) is the gold standard for treating aortic valve stenosis.[3] It is a major operation that requires opening the chest and using a heart-lung bypass machine, but the risks associated with SAVR are far less than those of leaving severe aortic valve stenosis untreated.[4-6] In this operation, the damaged valve is removed and replaced with a new

valve. In most patients, heart function improves dramatically soon after surgery. Once patients complete the early stages of recovery, which may take a few months, they feel significant improvements in their symptoms and quality of life.

A recent study[1] examined long-term survival in 145,911 patients aged 65 years and older who underwent SAVR in one of the 1,026 centres that participated in the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery registry in the United States and Canada between 1991 and 2007. This study provided detailed benchmarks for long-term survival after SAVR. Data were stratified by age, and perioperative risk of death was calculated using STS risk scores. The categories of surgical risk were based on original proposed thresholds: patients were at high risk if their STS scores were 10% or more, at intermediate risk if their STS scores were 5% to 9.9%, and at low risk if their STS scores were less than 5%. (More recently, and after TAVI was introduced into clinical practice, these thresholds were modified and cut-off points were lowered.[7]) This study[1] found that patients with a low STS risk score (< 5%) had excellent long-term survival after SAVR. At 4 years, survival in low-risk patients aged 80 years and older was 75.1%. Four-year survival rates in patients aged 80 years and older at intermediate risk and high risk were 57.6% and 40%, respectively. Figure 1 shows long-term survival rates after SAVR by age and risk category.

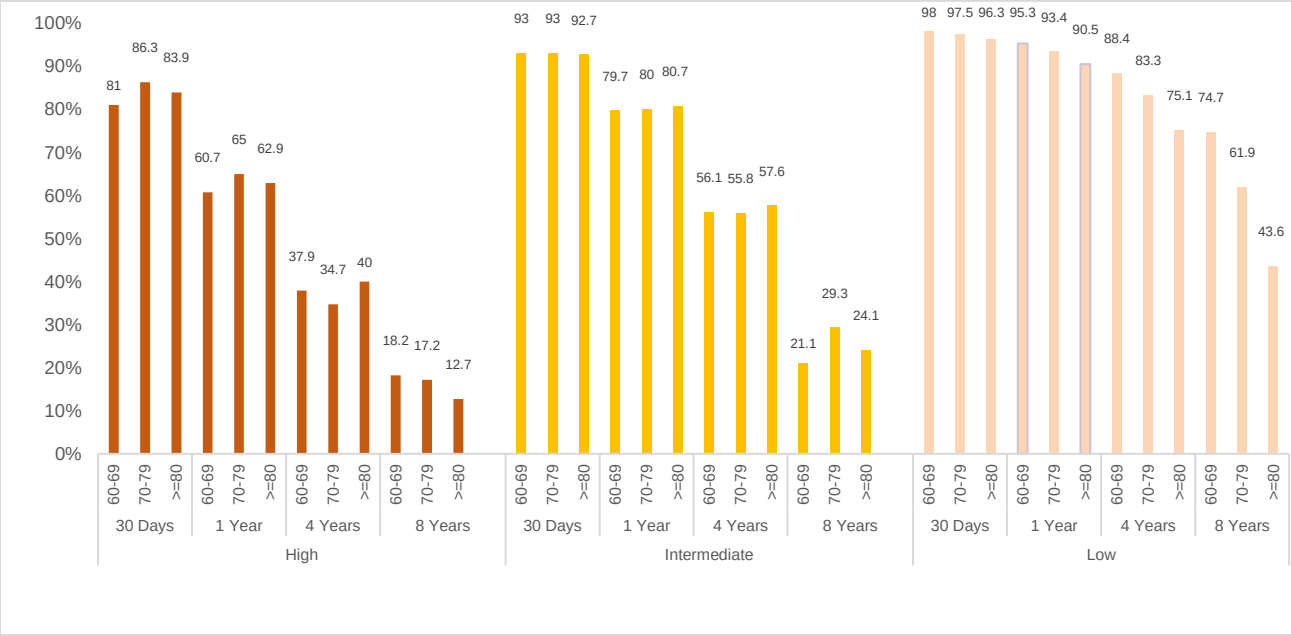

Figure 1: Survival After SAVR, Stratified by Age and Risk Category

Abbreviation: SAVR, surgical aortic valve replacement.
Source: Data from Brennan et al.[1]

These data[1] also showed that age alone was not a contraindication for SAVR, and that SAVR could be performed in the elderly with acceptable rates of mortality and morbidity.

Another study showed that patients older than 80 years of age with severe aortic valve stenosis also benefitted from surgical valve replacement. One-year, 2-year, and 5-year survival rates among patients who underwent SAVR were 87%, 78%, and 68%, respectively, and among patients who did not have SAVR were 52%, 40%, and 22%, respectively ($P < .001$).[6]

Balloon Aortic Valvuloplasty

For patients with severe aortic valve stenosis who cannot undergo SAVR or are unwilling to have the procedure, medical therapy and balloon aortic valvuloplasty (BAV) are the only other options. However, these treatments are largely ineffective for long-term management.[8,9]

BAV is a palliative procedure: it can provide immediate improvement in symptoms, but only temporarily. For many years, BAV has been used to treat elderly patients with severe aortic valve stenosis who were too ill to undergo cardiac surgery. In younger patients with abnormal valve leaflets who develop aortic valve stenosis, acute and intermediate-term results are good with BAV.[9] However, in older patients, in whom degenerative aortic valve stenosis is the most common cause, the acute clinical and hemodynamic benefits of BAV are not lasting, and restenosis (return of the blockage) occurs in most patients within 6 months.[9] In fact, the effectiveness of BAV is apparent only in patients with normal left ventricular function, and they are generally candidates for surgical valve replacement anyway.[9]

A study based on registry data has shown high rates of mortality and in-hospital complications after BAV.[10,11] Long-term survival after BAV was poor, and early restenosis and recurrent hospitalizations were common. Thirty-day mortality was substantial, at 14%. Survival at 1 year, 2 years, and 3 years was 55%, 35%, and 23%, respectively, and most deaths were due to cardiac causes. The rate of in-hospital complications was 54% and included transfusion (23%), cardiac death (8%), vascular surgery (7%), cerebrovascular accident (3%), cardiogenic shock (3%), and other complications (10%).[10] In this study, hospitalization rates were also high after BAV (64%): 32% of patients had three or more subsequent hospitalizations. The authors raised concerns about the appropriateness of BAV in patients who exhibit high-risk characteristics, and some investigators believe that BAV should be used only as a “bridge” to SAVR or in patients with severe aortic valve stenosis who require emergency noncardiac surgery.

Transcatheter Aortic Valve Implantation

Over the last decade, transcatheter aortic valve implantation (TAVI) has emerged as an effective and less invasive treatment option for patients who are not suitable candidates for surgery and as an alternative to SAVR in patients with severe aortic valve stenosis who are at high risk of mortality and morbidity after SAVR.[12,13] Results from randomized controlled trials have provided a basis for evaluating TAVI in patients in these surgical risk categories.[14,15]

Patients with severe aortic valve stenosis who seek treatment have their baseline operative risk estimated using the STS risk score or EuroSCORE. Based on the risk estimate, the treating physician and the heart team choose SAVR or TAVI, as well as the method of transcatheter valve insertion, if TAVI is chosen.

Technology

The TAVI procedure involves implanting a bioprosthetic valve using a catheter. This procedure does not require a heart-lung bypass machine to support blood circulation. It is most often performed using a transfemoral approach, inserting the delivery catheter through the femoral artery. Factors that may exclude the transfemoral approach include the inside diameter of artery, if the artery is twisted, or if there is too much blockage. The inside diameter of the artery needs to be more than the diameter of the TAVI delivery system, or the artery could be damaged.[16]

If transfemoral TAVI is not feasible, other arteries may be used as entry sites (e.g., the subclavian artery, the common carotid artery, or direct to the aorta). A transapical approach can also be used, where TAVI is performed using an incision in the chest. Then, the new valve is inserted through the left ventricle of the heart.

Ideally, TAVI is performed in a hybrid operating room that has advanced multimodality imaging and can accommodate the equipment and people needed for both TAVI and open-heart surgery. For best results, TAVI requires a multidisciplinary team, including a heart surgeon, an interventional cardiologist (a doctor with special training in catheter-based heart procedures), and a cardiac anesthesiologist who has experience in echocardiography. It is usually performed under general anesthesia, or occasionally under sedation with local anesthesia.

Possible complications from TAVI include injury to the artery used to implant the new valve; paravalvular aortic regurgitation (some of the blood pumped out of the heart leaks back in); blockage in the coronary artery; damage to the mitral valve (one of the other heart valves); cardiac perforation (a hole in the heart); abnormal heart rhythm; and stroke.[16]

Regulatory Information

The TAVI device and delivery system have improved rapidly over the past few years, and different valves and delivery systems have been developed. About 10 different valves have been granted a CE Mark in Europe. The Edwards SAPIEN (balloon-expandable) and Medtronic CoreValve (self-expandable) systems have been granted licences in Canada. The first-generation SAPIEN valve has been replaced with second- and third-generation valves (SAPIEN XT THV and SAPIEN 3).

Table 1 describes the transcatheter aortic valves that have been granted licenses for use in Canada, as well as those that are in commercial use in other countries or are at different stages of clinical trials.

Table 1: Transcatheter Aortic Valves and Health Canada Licensing Status

Aortic Valve	Manufacturer	Licensed in Canada (Licence Number)
Edwards SAPIEN THV (first-generation) 	Edwards Lifesciences, Irwin, CA	Yes (86404)
Edwards SAPIEN XT THV (second-generation) 	Edwards Lifesciences, Irwin, CA	Yes (92081)
Medtronic CoreValve 	Medtronic Inc., Minneapolis, MN	Yes (89391)
Edwards SAPIEN 3 (third-generation)	Edwards Lifesciences, Irwin, CA	No
Edwards CENTERA	Edwards Lifesciences, Irwin, CA	No
Lotus	Boston Scientific Corporation, Marlborough, MA	No
Symetis Acurate	Symetis, Ecublens, Switzerland	No
Direct Flow (nonmetallic device)	Direct Flow Medical, Santa Rosa, CA	No
Portico	St. Jude Medical Inc., St. Paul, MN	No
CoreValve Engager	Medtronic Inc., Minneapolis, MN	No
CoreValve Evolute R	Medtronic Inc., Minneapolis, MN	
JenaValve	JenaValve Technology, Munich, Germany	No
Trinity TAVI System	Transcatheter Technologies GmbH, Regensburg, Germany	No

The transcatheter aortic valves and delivery systems for both SAPIEN and CoreValve have undergone a number of iterative changes over the past few years. The new valves have improved sealing mechanisms and ease of positioning or retrieving. The new delivery systems have a smaller catheter diameter to minimize the risk of vascular complications. Clinical trials (PARTNER II and SURTAVI) are underway to provide evidence of the effectiveness and safety of the new-generation SAPIEN and CoreValve devices.

Context

The first TAVI procedure in Ontario was performed in 2007. The Cardiac Care Network of Ontario began capturing data on TAVI procedures in the Cardiac Care Network Cardiac Registry in 2009, and information about cases performed before 2009 were collected retrospectively. Before the device was licensed in Canada, TAVI was provided to patients under the Health Canada Special Access Program. Between January 2007 and November 2013, 1,128 TAVI procedures were performed in Ontario.

In 2007, there were only two TAVI programs in Ontario, but over time other hospitals have begun to establish their own. There are now 10 TAVI programs in 10 cardiac centres in Ontario. In 2013, the Ontario Ministry of Health and Long-Term Care requested that the Cardiac Care Network conduct a comprehensive field evaluation of TAVI programs in Ontario.

Research Questions

- What is the effectiveness of TAVI compared with SAVR or medical management with BAV in terms of symptom relief, quality of life, mortality, and adverse events for patients with severe aortic valve stenosis?
- What is the cost-effectiveness of TAVI compared with SAVR in high-risk patients with severe aortic stenosis?
- What is the budget impact of implementing TAVI over the next 5 years from the perspective of the Ontario Ministry of Health and Long-Term Care?

CLINICAL EVIDENCE REVIEW

Objective

The objective of this clinical evidence review was to assess the effectiveness of TAVI compared with SAVR or medical management with BAV in patients with severe aortic valve stenosis.

Methods

Research questions were developed by Health Quality Ontario in consultation with experts.

Sources

We performed a literature search on September 30, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, EBM reviews, and National Health Service (NHS) Economic Evaluation Database, for studies published from January 1, 2011, to September 30, 2015.

Our previous health technology assessment for the safety, effectiveness, and cost-effectiveness of TAVI[14] included studies published up to September 11, 2012. In this review, we included studies from the previous review.

Search strategies were developed by medical librarians using medical subject headings (MESH). See Appendix 1 for full details, including all search terms.

Literature Screening

A single reviewer reviewed the abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles. Studies were screened for eligibility according to the inclusion/exclusion criteria. We also examined reference lists for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2011, and September 30, 2015
- Randomized controlled trials
- Studies that reported the clinical outcomes of TAVI, including mortality, important cardiovascular outcomes (such as stroke, myocardial infarction, aortic regurgitation, vascular complications, bleeding), and adverse events in comparison with SAVR or medical management with BAV
- Studies that investigated quality of life or patient preference

Exclusion Criteria

- Nonrandomized trials
- Studies reporting on technical aspects of different prostheses, design of TAVI systems, or techniques for valve implantation

- Studies reporting on combined strategies, such as a combination of TAVI and other cardiac procedures
- Studies reporting on the outcomes of implantation of a second valve

Outcomes of Interest

- Effectiveness
  - New York Heart Association (NHYA) functional class
  - Quality of life
- Safety
  - All-cause and cardiovascular mortality
  - Risk of adverse events (aortic regurgitation, stroke, major vascular complications, major bleeding, need for pacemaker insertion, myocardial infarction, renal failure)

Data Extraction

We extracted relevant data on study characteristics, risk of bias items, and outcomes using a standardized data form. The form collected information about:

- Source (i.e., citation information)
- Methods (i.e., sequence generation, participant allocation, allocation concealment, blinding, loss to follow-up, reporting of important outcomes)
- Outcomes (as above)

Statistical Analysis

The populations included in these studies had different levels of risk according to mean Society of Thoracic Surgeons (STS) surgical risk scores. The STS score is an estimate of the risk of mortality from the surgical procedure. Due to the variations in mean STS mean scores across studies, we did not perform a meta-analysis to pool data. Instead, we present the results separately for each trial by mean STS score.

We used the Kaplan-Meier percentages and *P*-values reported by the authors. We used STATA version 11 (StataCorp LP, College Station, TX) for graphical presentation of the data in each risk category.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[17] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology. See Appendix 2 for full details of the GRADE analysis.

Expert Consultation

In August 2015, we sought expert consultation for this clinical review. Members of the consultation were physicians in the specialty areas of cardiac surgery and interventional cardiology. The role of the expert advisors was to assist in framing the research questions, provide information about current practices and devices in use, and offer advice. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

Results

Literature Search

The database search yielded 493 citations published between January 1, 2011, and September 30, 2015. After removing duplicates, we reviewed titles and abstracts to identify potentially relevant articles. We obtained the full texts of these articles for further assessment. Eighteen citations (all randomized controlled trials) met the inclusion criteria. We hand-searched the reference lists of the included citations, along with health technology assessment websites and other sources, to identify additional relevant citations, and one new study was included in the final 18.

Figure 2 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

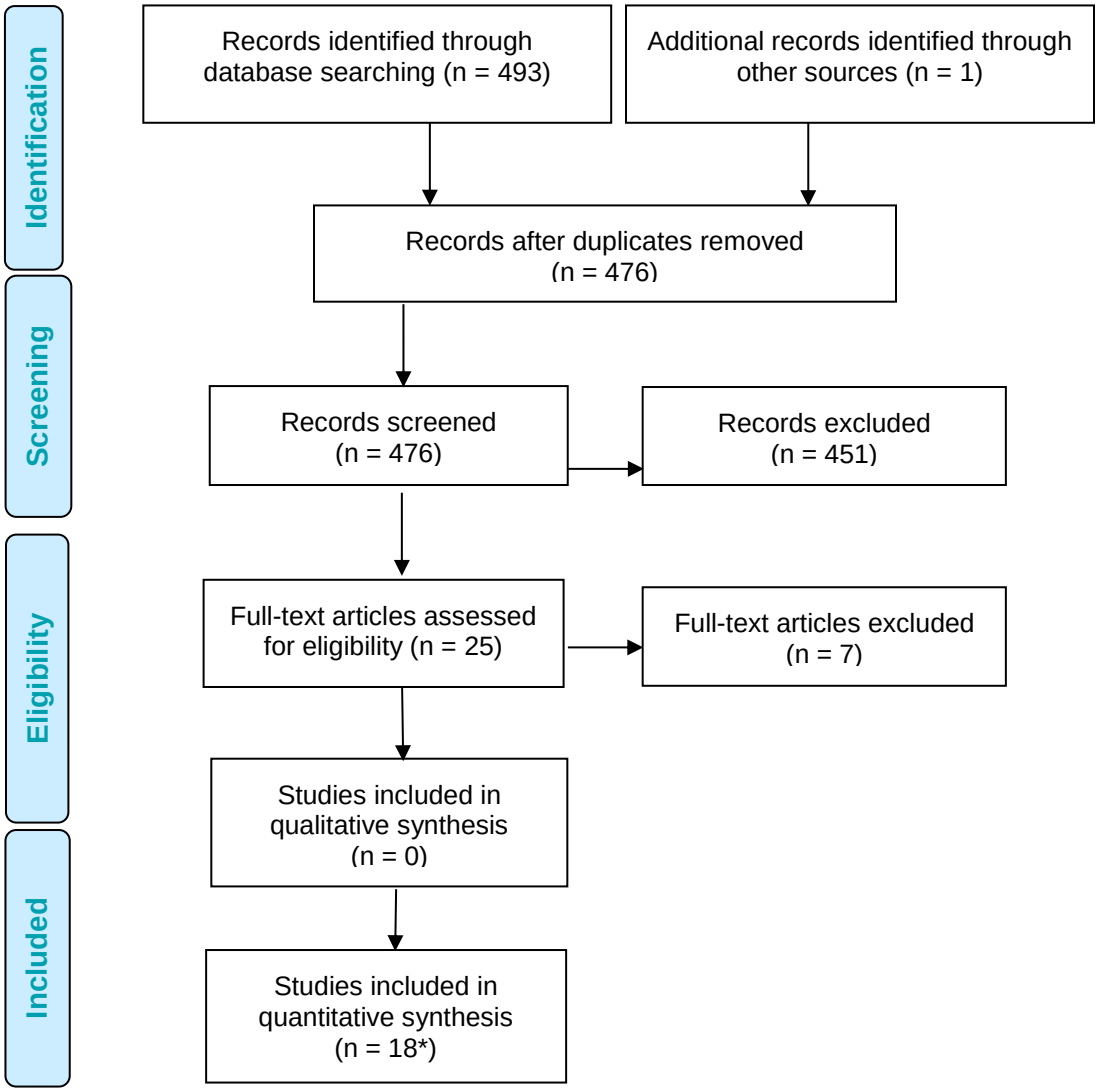

Figure 2: PRISMA Flow Diagram

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
*From five trials.
Source: Adapted from Moher et al.[18]

The 18 included citations reported on five studies and were either original articles, reports on different outcomes, or reports of follow-up data.

The PARTNER (Placement of Aortic Transcatheter Valve) trial included two cohorts: A and B.[19,20] Patients in both cohorts were considered high-risk for cardiac surgery. The prosthetic valve used in both PARTNER trials was the Edwards SAPIEN valve. Patients in cohort A (n = 699) were eligible for SAVR despite their high-risk status (mean STS: TAVI ,11.8%; SAVR, 11.7%). Patients assigned to TAVI from this cohort were first considered for the transfemoral approach, but if this was not feasible, they were treated using the transapical approach. Patients assigned to SAVR were stratified according to whether a transfemoral or transapical approach would have been used had they been assigned to TAVI.

Patients in PARTNER cohort B had specific coexisting conditions and were deemed unsuitable for SAVR.[19] Cohort B compared transfemoral TAVI with BAV and included 358 patients at high risk who also had coexisting conditions that contributed to the surgeon's determination of unsuitability for surgery. The conditions were as follows: porcelain aorta (15.1%), chest deformity or chest wall irradiation (13.1%), oxygen-dependent respiratory insufficiency (23.5%), or frailty (23.1%). The PARTNER trial cohort B[19] tested the hypothesis that transfemoral TAVI was superior to medical management with BAV. Patients were randomly assigned to either TAVI (n = 179) or BAV (n = 179). Baseline characteristics of the patients in the two arms were similar, except that significantly more patients in the BAV arm had chronic obstructive pulmonary disease or atrial fibrillation and more patients in the TAVI arm had porcelain aorta. During the first year, 84% of the patients in the medical management arm underwent BAV. The majority of BAV interventions (64%) were performed within 30 days after randomization.

The US CoreValve trial[21] included 795 patients (mean STS score 7%). Patients were randomized to transarterial TAVI or SAVR. A total of 83% of patients were eligible for transfemoral TAVI, and 17% required access via the subclavian artery or directly through the aorta (nontransfemoral TAVI group). Patients who underwent nontransfemoral TAVI had more cardiac comorbidities and peripheral vascular disease than those who underwent transfemoral TAVI.

The NOTION (Nordic Aortic Valve Intervention) trial[22] included 280 low-risk patients (STS scores of approximately 3%). This study had only 1 year of follow-up. The STACCATO (Surgical Aortic Valve Replacement [AVR] in Operable Elderly Patients With Aortic Stenosis) trial[23] also included low-risk patients who underwent transapical TAVI or SAVR, but it was terminated prematurely due to high incidence of major adverse events in the transapical TAVI group.

The trials included patient populations at different levels of surgical risk. In addition, the devices used in the trials were different, making it a challenge to interpret the results in some instances. Studies used the original STS risk score to determine the risk of death within 30 days after SAVR. In PARTNER cohort A,[20] determination of risk was made by surgeons at each study centre, and patients with an STS score of 10% or more were included. The mean STS score for the patients in this trial was approximately 12%, and the authors described their study population "at high risk for SAVR." However, according to the modified STS risk threshold,[7] this population fell in the "extreme risk" category. In the US CoreValve trial,[21] surgical risk assessment included STS scores and other factors not included in the STS assessment. The mean STS score in this trial was about 7%, but the authors described their study population "at increased risk of surgery" because of additional factors that they thought would increase the risk of SAVR.

Table 2 describes the characteristics of the five TAVI trials.

Table 2: Studies Comparing Outcomes of TAVI With Other Procedures

Author, Year	Trial Name	Patients, N	Mean Age, years (SD)	Mean STS Score (SD)	Logistic Euro Score (SD)	Transcatheter Valve	Implantation Route	Follow-up
Leon et al, 2010[19] Reynolds et al, 2011[24] Makkar et al, 2012[13] Kapadia et al, 2014[25] Svensson et al, 2014[26] Douglas et al, 2015[27] Kapadia et al, 2015[28]	PARTNER Cohort B	358 TAVI: 179 BAV: 179	TAVI: 83.1 (8.6) SAVR: 83.2 (8.3) *P* = .95	TAVI: 11.2 (5.8) SAVR: 12.1 (6.1) *P* = .14	TAVI: 26.4 (17.2) SAVR: 30.4 (19.1) *P* = .04	Edwards SAPIEN	Transfemoral	5 years
Smith et al, 2011[20] Kodali et al, 2012[12] Miller et al, 2012[29] Reynolds et al, 2012[30] Svensson et al, 2014[26] Hahn et al, 2013[31] Mack et al, 2015[32]	PARTNER Cohort A	699 TAVI: 348 SAVR: 351	TAVI: 83.6 (6.8) SAVR: 84.5 (6.4) *P* = .07	TAVI: 11.8 (3.3) SAVR: 11.7 (3.5) *P* = .61	TAVI: 29.3 (16.5) SAVR: 29.2 (15.6) *P* = .93	Edwards SAPIEN	Transfemoral and transapical	5 years
Adams et al, 2014[21] Arnold et al, 2015[33] Reardon et al, 2015[34]	US CoreValve	795 TAVI: 394 SAVR: 401	TAVI: 83.2 (7.1) SAVR: 83.3 (6.3) *P* = .80	TAVI: 7.3 (3.0) SAVR: 7.5 (3.2) *P* = .34	TAVI: 17.6 (13.0) SAVR: 18.4 (12.8) *P* = .24	CoreValve	Transfemoral and non-transfemoral	2 years
Thyregod et al, 2015[22]	NOTION	280 TAVI: 145 SAVR: 135	TAVI: 79.2 (4.9) SAVR: 79.0 (4.7)	TAVI: 2.9 (1.6) SAVR: 3.1 (1.7)	TAVI: 8.4 (4.0) SAVR: 8.9 (5.5)	CoreValve	Transfemoral	1 year
Nielsen et al, 2012[23]	STACCATO	70 TAVI: 34 SAVR: 36	TAVI: 80 (3.6) SAVR: 82 (4.4) *P* = .15	TAVI: 3.1 (1.5) SAVR: 3.4 (1.2) *P* = .43	TAVI: 9.4 (3.9) SAVR: 10.3 (5.8) *P* = .25	Edwards SAPIEN	Transapical	3 months, study terminated prematurely

Abbreviations: BAV, balloon aortic valvuloplasty; SAVR; surgical aortic valve replacement; SD, standard deviation; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

Methodological Quality of the Included Studies

Complete results of the methodology checklist for included studies are presented in Appendix 2. A total of 18 citations (5 studies) were deemed directly applicable to the research question. The methodological quality of these studies was assessed: for adverse events, all four of the included studies had minor limitations; for quality of life, three had potentially serious limitations.

Results for Effectiveness

To measure the effectiveness of the interventions, we considered patients' functional ability, as measured by NYHA functional class, and changes in quality-of-life scores among survivors (Tables 3 to 6). The GRADE evidence profile for effectiveness is presented in Table 7.

Table 3: Functional Outcomes After TAVI or SAVR in PARTNER Trial, Cohort A, Intention-to-Treat Analysis[a]

Author, Year	NYHA Functional Class I/II Among Survivors, N (%)	Quality of Life, Mean (SD)			
		KCCQ Summary	SF-12 Physical	SF-12 Mental	EQ-5D Utilities
Baseline Smith et al, 2011[20] Reynolds et al, 2012[30]	TAVI: 20 (5.7) SAVR: 21 (6.0)	TF-TAVI: 39.3 (21.7) SAVR: 43.8 (22.6) TA-TAVI: 40.3 (22.1) SAVR: 46.2 (19.8)	TF-TAVI: 29.7 (7.7) SAVR: 30.6 (8.1) TA-TAVI: 29.4 (7.4) SAVR: 31.7 (8.5)	TF-TAVI: 47.0 (11.5) SAVR: 47.1 (11.0) TA-TAVI: 46.6 (11.4) SAVR: 48.7 (9.6)	TF-TAVI: 0.66 (0.2) SAVR: 0.66 (0.21) TA-TAVI: 0.67 (0.19) SAVR: 0.72 (0.17)
		Mean Change From Baseline (95% CI)			
30 days Smith et al, 2011[20] Kodali et al, 2012[12] Reynolds et al 2012[30]	TAVI: NA (75) SAVR: NA (65)	TF-TAVI: 23.7 (20.1–27.3) SAVR: 12.1 (7.4–16.7) TA-TAVI: 12.5 (6.1–19.0) SAVR: 12.5 (5.5–19.5)	TF-TAVI: 5.0 (3.5–6.4) SAVR: 2.6 (0.7–4.4) TA-TAVI: 2.8 (0.6–5.0) SAVR: 0.5 (–2.1 to 3.0)	TF-TAVI: 4.3 (2.5–6.1) SAVR: –0.3 (–2.6 to 2.1) TA-TAVI: –0.8 (–3.7 to 2.2) SAVR: 1.7 (–1.4 to 4.8)	TF-TAVI: 0.08 (0.04–0.11) SAVR: 0.02 (–0.02 to 0.06) TA-TAVI: –0.02 (–0.08 to 0.03) SAVR: 0.01 (–0.04 to 0.06)
1 year Smith et al, 2011[20] Reynolds et al, 2012[30] Mack et al, 2015[32]	TAVI: 212/250 (84.8) SAVR: 196/226 (86.7)	TF-TAVI: 28.7 (24.4–33.1) SAVR: 26.8 (21.8–31.7) TA-TAVI: 29.6 (23.2–36.1) SAVR: 21.6 (13.8–29.4)	TF-TAVI: 6.3 (4.5–8.2) SAVR: 6.1 (4.2–8.1) TA-TAVI: 7.1 (4.5–9.8) SAVR: 4.5 (1.2–7.8)	TF-TAVI: 5.0 (3.1–7.0) SAVR: 4.7 (2.4–6.9) TA-TAVI: 3.6 (0.1–7.0) SAVR: 3.9 (0.6–7.2)	TF-TAVI: 0.09 (0.05–0.12) SAVR: 0.08 (0.04–0.12) TA-TAVI: 0.06 (0.01–0.12) SAVR: 0.05 (–0.02 to 0.12)
2 years Kodali et al, 2012[12] Hahn et al, 2013[31]	TAVI: NA (83.9) SAVR: NA (85.2)	NA	NA	NA	NA
5 years Mack et al, 2015[32]	TAVI: 85/100 (85.0) SAVR: 79/97 (81.4)	NA	NA	NA	NA

Abbreviations: CI, confidence interval; EQ-5D, EuroQOL 5-dimension questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not available; NYHA, New York Heart Association; SD, standard deviation; SF-12, 12-item Short Form questionnaire; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
[a]Echocardiographic data (aortic regurgitation) were based on as-treated analysis. Quality-of-life data were estimated using random-effects growth curve models as reported by the author.

Table 4: Functional Outcomes After TAVI or SAVR in US CoreValve Trial, As-Treated Analysis[a]

Author, Year	NYHA Functional Class I/II Among Survivors, %	Quality of Life, Mean (SD)			
		KCCQ Summary	SF-12 Physical	SF-12 Mental	EQ-5D Utility
Baseline	TAVI: 16.9	**Iliofemoral**	**Iliofemoral**	**Iliofemoral**	**Iliofemoral**
Adams et al, 2014[21]	SAVR: 18.2	TAVI: 45.9 (23.6)	TAVI: 30.6 (9.0)	TAVI: 47.0 (12.3)	TAVI: 0.73 (0.2)
Arnold et al, 2015[33]		SAVR: 46 (22.4)	SAVR: 30.7 (8.4)	SAVR: 48.7 (11.6)	SAVR: 0.73 (0.17)
Reardon et al, 2015[34]		**Non-iliofemoral**	**Non-iliofemoral**	**Non-iliofemoral**	**Non-iliofemoral**
		TAVI: 51.5 (22.1)	TAVI: 31.4 (10.1)	TAVI: 49.5 (10.5)	TAVI: 0.76 (0.14)
		SAVR: 51.2 (21.0)	SAVR: 32.8 (9.0)	SAVR: 46.8 (11.7)	SAVR: 0.72 (0.21)
		Mean Change From Baseline (95% CI)			
30 days	TAVI: 86.2	**Iliofemoral**	**Iliofemoral**	**Iliofemoral**	**Iliofemoral**
Adams et al, 2014[21]	SAVR: 76.5	TAVI: 21.6 (17.7–25.5)	TAVI: 5.4 (4.0–6.9)	TAVI: 3.5 (1.7–5.4)	TAVI: 0.055 (0.024–0.087)
Arnold et al, 2015[33]		SAVR: 3.5 (–1.0 to 7.9)	SAVR: 0.0 (–1.7 to 1.7)	SAVR: –2.9 (–5.1 to –0.7)	SAVR: –0.073 (–0.116 to –0.033)
Reardon et al, 2015[34]		**Non-iliofemoral**	**Non-iliofemoral**	**Non-iliofemoral**	**Non-iliofemoral**
		TAVI: 3.3 (–7.3 to 13.9)	TAVI: 1.7 (–2.4 to 5.8)	TAVI: –2.8 (–8.1 to 2.4)	TAVI: –0.082 (–0.178 to 0.014)
		SAVR: 5.4 (–6.2 to 17.0)	SAVR: –1.0 (–5.7 to 3.7)	SAVR: 0.4 (–6.2 to 7.0)	SAVR: –0.072 (–0.171 to 0.027)
1 year	TAVI: 94.5	**Iliofemoral**	**Iliofemoral**	**Iliofemoral**	**Iliofemoral**
Adams et al, 2014[21]	SAVR: 93.2	TAVI: 24.0 (20.6–27.5)	TAVI: 5.9 (4.2–7.5)	TAVI: 4.8 (3.0–6.5)	TAVI: 0.043 (0.015–0.071)
Arnold et al, 2015[33]		SAVR: 21.8 (17.5–26.0)	SAVR: 5.1 (3.4–6.7)	SAVR: 2.9 (0.9–4.9)	SAVR: 0.003 (–0.029 to 0.035)
Reardon et al, 2015[34]		**Non-iliofemoral**	**Non-iliofemoral**	**Non-iliofemoral**	**Non-iliofemoral**
		TAVI: 18.7 (9.2–28.1)	TAVI: 6.6 (2.4–10.8)	TAVI: 3.0 (–0.6 to 6.7)	TAVI: 0.023 (–0.033 to 0.080)
		SAVR: 22.7 (14.5–30.8)	SAVR: 6.1 (2.1–10.2)	SAVR: 4.8 (–0.2 to 9.9)	SAVR: 0.049 (–0.005 to 0.103)
2 years	TAVI: 92.1	NA	NA	NA	NA
Reardon et al, 2015[34]	SAVR: 90.5				

Abbreviations: CI, confidence interval; EQ-5D, EuroQOL 5-dimension questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not available; NYHA, New York Heart Association; SD, standard deviation; SF-12, 12-item Short Form questionnaire; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]Quality-of-life data are based on intention-to-treat analysis.

Table 5: Functional Outcomes After TAVI or SAVR in Low-Risk Patients: As-Treated Analysis

Author, Year	NYHA Functional Class I/II Among Survivors, %	Quality of Life, SF-12, Mean (SD)	
TF-TAVI vs. SAVR			
Baseline Thyregod et al, 2015[22]	TAVI: 52.5 SAVR: 54.9	NA	
3 Months Thyregod et al, 2015[22]	TAVI: 94.8 SAVR: 96.6		
1 Year Thyregod et al, 2015[22]	TAVI: 96.9 SAVR: 96.7		
TA-TAVI vs. SAVR			
Baseline Nielsen et al, 2012[23]	TAVI: 16 SAVR: 20	**Physical** TAVI: 35 (10) SAVR: 37 (12) *P* = .48	**Mental** TAVI: 47 (10) SAVR: 46 (17) *P* = .66
3 Months Nielsen et al, 2012[23]	TAVI: 26 SAVR: 32 *P* = .16	**Physical** TAVI: 42 (14) SAVR: 43 (15) *P* = .91	**Mental** TAVI: 53 (14) SAVR: 50 (17) *P* = .44

Abbreviations: NA, not available; NYHA, New York Heart Association; SD, standard deviation; SF-12, 12-item Short Form questionnaire; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.

Table 6: Functional Outcomes After TAVI or BAV in Patients Who Were Not Suitable Candidates for Cardiac Surgery: Intention-to-Treat Analysis[a]

Author, Year	NYHA Functional Class I/II Among Survivors, %	Quality of Life, Mean (SD)		
		KCCQ Summary	SF-12 Physical	SF-12 Mental
Baseline	TAVI: 7.8 BAV: 6.1 *P* = .60	TAVI: 36.2 (20.5) BAV: 34.4 (20.1) *P* = .44	TAVI: 28.2 (7.7) BAV: 27.7 (6.9) *P* = .54	TAVI: 44.5 (12.2) BAV: 45.2 (11.0) *P* = .57
30 days Leon et al, 2010[19] Reynolds et al, 2011[24] Douglas et al, 2015[27]	NA	TAVI: 61.6 (26.2) BAV: 49.2 (24.3)	TAVI: 34.6 (10.3) BAV: 30.2 (7.3)	TAVI: 47.9 (11.0) BAV: 48.5 (10.9)
1 year Reynolds et al, 2011[24] Kapadia et al, 2014[25] Douglas et al, 2015[27]	TAVI: 76.3 BAV: 50 *P* < .0001	TAVI: 69.4 (25.3) BAV: 47.0 (24.6)	TAVI: 34.9 (11.1) BAV: 29.7 (8.5)	TAVI: 53.3 (10.0) BAV: 46.6 (11.7)
2 years Kapadia et al, 2014[25] Douglas et al, 2015[27]	NA	NA	NA	NA
3 years Kapadia et al, 2014[25] Douglas et al, 2015[27]	TAVI: 70 BAV: 50 *P* = .24	NA	NA	NA
5 years Kapadia et al, 2015[28]	TAVI: 85.7 SAVR: 60 *P* = .53	NA	NA	NA

Abbreviations: BAV, balloon aortic valvuloplasty; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not available; NYHA, New York Heart Association; SF-12, 12-item Short Form questionnaire; SD, standard deviation; TAVI, transcatheter aortic valve implantation.
[a]Echocardiographic data (aortic regurgitation) were based on as-treated analysis. Quality-of-life data were estimated using random-effect growth curve models as reported by the author.

Table 7: GRADE Evidence Profile for Effectiveness, Comparison of TAVI and SAVR

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
NYHA Functional Class							
4 (RCTs)	No serious limitations	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Quality of Life							
3 (RCTs)	Serious limitations (–2)[a]	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]High rate of missing data at baseline and follow-up. Assessments were unblinded.

New York Heart Association Functional Class

New York Heart Association functional class places patients in one of four categories based on their level of limitation during physical activities measured by NYHA scores: 75–100 (class I); 60–74 (class II); 45–59 (class III); and 0–44 (class IV).[35] Trials of high-risk and intermediate-risk patients included those who were in NYHA functional class of II or more. The trial of low-risk patients also included patients who were in NYHA functional class I (TAVI: 4.9%; SAVR: 2.2%).[22]

In the PARTNER A[20] and US CoreValve trials,[21] NYHA functional class among survivors improved with both TAVI and SAVR and persisted for at least 2 years (Figure 3). Comparison of the data from baseline to 2 years in these patients indicated that patients who received TAVI or SAVR benefitted equally from the two interventions. However, a trial of low-risk patients[22] showed that patients who underwent TAVI had significantly more dyspnea than the SAVR group at 1 year (P = .01).

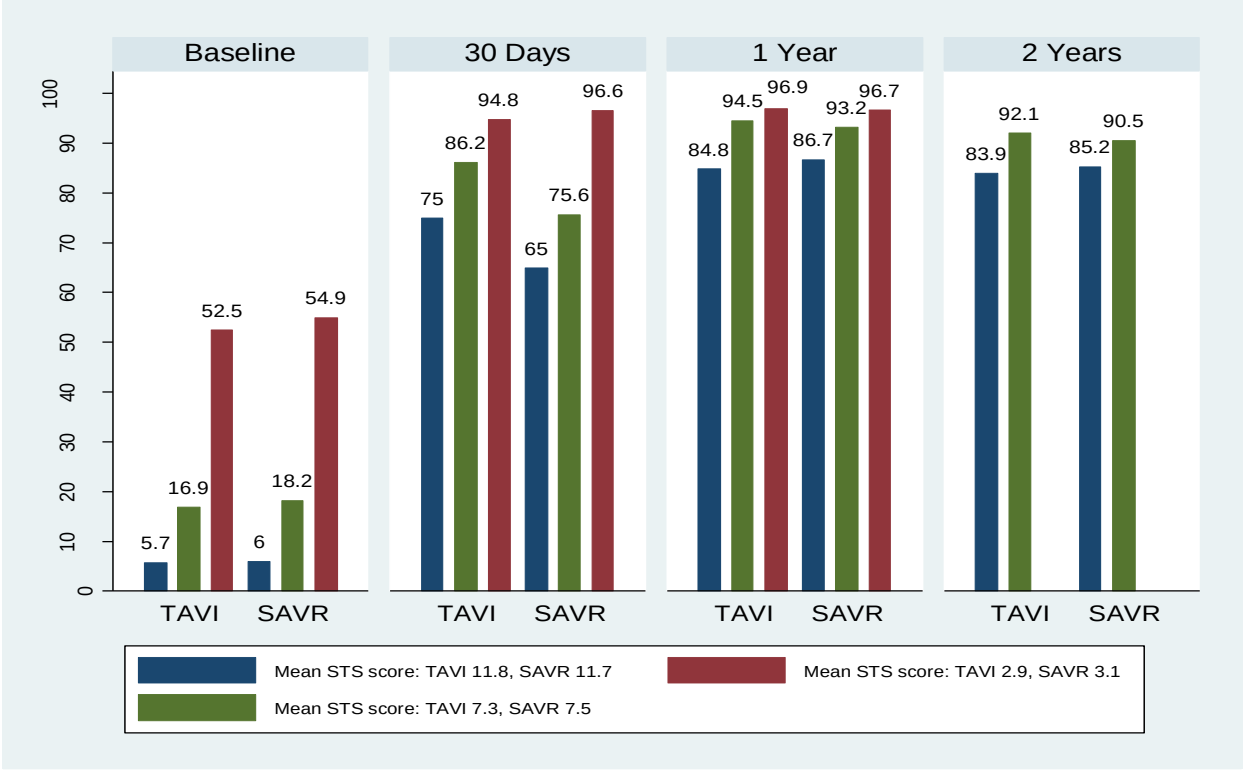

Figure 3: NYHA Functional Class I and II Among Survivors, TAVI vs. SAVR

Abbreviations: NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
Sources: Data from Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] Mack et al,[32] and Reardon et al.[34]

In cohort B of the PARTNER trial, which included patients who were not suitable candidates for surgery, only a small proportion of the patients in the transfemoral TAVI and BAV groups were in NYHA functional class II before the intervention.[19] At 1 year, most patients in the transfemoral TAVI arm and half of the patients in the BAV arm had a NYHA functional class of I or II (Figure 4).

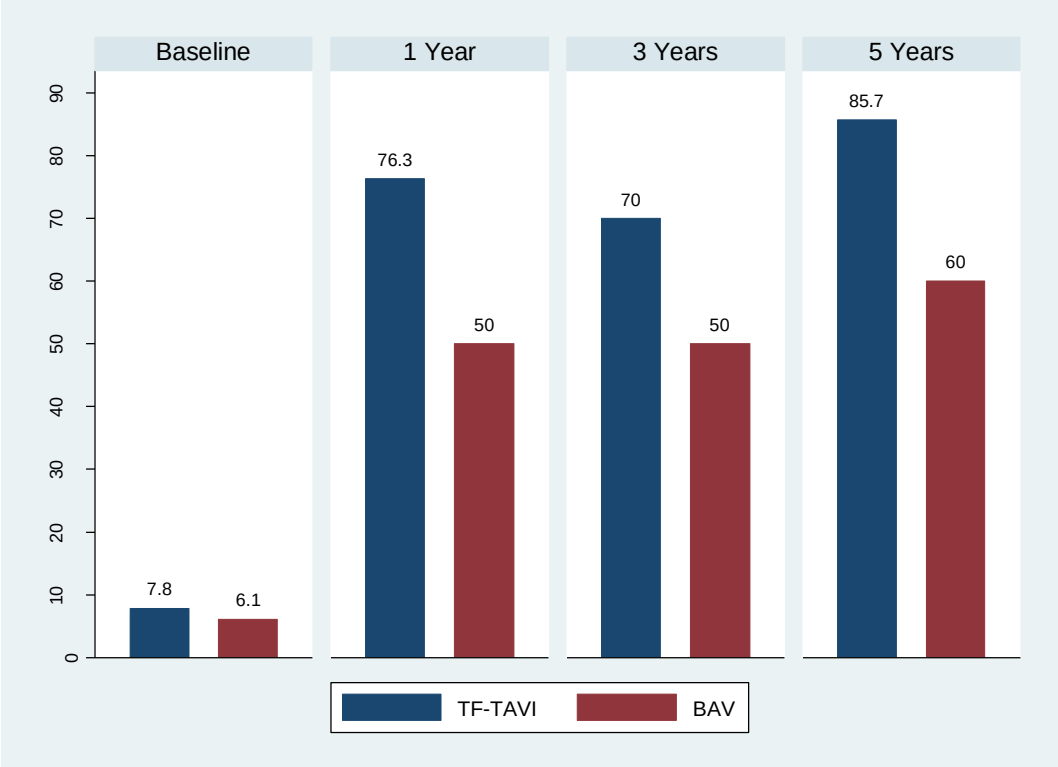

Figure 4: NYHA I/II Among Survivors, Transfemoral TAVI vs. BAV in Patients Who Were Not Suitable Candidates for Cardiac Surgery

Abbreviations: BAV, balloon aortic valvuloplasty; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
Sources: Data from Leon et al,[19] Kapadia et al,[25] Douglas et al,[27] and Kapadia et al.[28]

Quality of Life

Patients' quality of life was measured using both disease-specific and generic questionnaires. Disease-specific health status was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ).[36] The KCCQ includes four subscales (physical limitation, total symptoms, quality of life, and social limitation). The combination of these subscales forms an overall summary score. Values for all KCCQ domains and the summary score range from 0 to 100, with higher scores indicating better quality of life. The KCCQ overall summary score generally correlates with NYHA functional class as follows: KCCQ 75 to 100, NYHA class I; KCCQ 60 to 74, NYHA class II; KCCQ 45 to 59, NYHA class III; KCCQ 0 to 44, NYHA class IV. Generally, 5-, 10-, and 20-point increases in scores correspond to small, moderate, or large clinical improvement, respectively.

All trials used the Short Form 12 (SF-12) health survey as a generic health status questionnaire.[37] This questionnaire includes physical and mental subscales, and higher scores indicate better quality of life. The minimal clinically important changes in the mental and physical summary scores are about 2 to 2.5 points.

The study in low-risk patients did not report on quality of life.[22]

PARTNER trial cohort A included patients at high risk and investigated two methods of valve implantation in two separate subgroups.[20] From 699 patients in the study, 628 (90%) completed the baseline KCCQ questionnaire. Patients with missing baseline KCCQ scores were excluded from the analysis. Follow-up questionnaires at each time point were obtained from more than 80% of the patients who survived. The difference between TAVI and SAVR was examined using longitudinal random-effect growth curve models.

Both TAVI and SAVR resulted in a great improvement in quality of life for these patients over the first year of follow-up. Patients who underwent transfemoral TAVI had a more rapid improvement than patients who underwent SAVR or transapical TAVI because of the slower recovery following either major surgery (SAVR) or thoracotomy (transapical TAVI). For the overall population, the adjusted mean difference (AMD) in KCCQ summary scores between TAVI and SAVR was in favour of TAVI at 1 month (AMD, 5.5; 95% CI, 1.2–9.8; *P* = .01). At 6 and 12 months, however, the AMD was in favour of SAVR (at 6 months: AMD, –2.6; 95% CI, –6.7 to 1.6 / at 12 months: AMD, –0.5; 95% CI, –4.8 to 3.8). The AMD at 6 and 12 months did not reach significance.

Since there was a significant interaction between treatment assignment and access site particularly at 1 month (*P* = .001), the authors reported quality of life separately for the transfemoral TAVI and transapical TAVI subcohorts, based on longitudinal growth curve models. In the transfemoral TAVI/SAVR subcohort, the AMD for KCCQ summary score was in favour of transfemoral TAVI only at 1 month (AMD, 9.9; 95% CI, 4.9–14.9; *P* < .001). At 6 and 12 months, the AMD was in favour of SAVR but did not reach significance (at 6 months: AMD, –0.5; 95% CI, –5.3 to 4.4; *P* = .85 / at 12 months: AMD, –1.2; 95% CI, –6.3 to 3.9; *P* = .64).

In the transapical TAVI/SAVR subcohort, the AMD for KCCQ summary score was in favour of SAVR at 1 month and 6 months (at 1 month: AMD, –5.8; 95% CI, –13.9 to 2.2; *P* = .15 / at 6 months: AMD, –7.9; 95% CI, –15.7 to 2.0; *P* = .04). There was no significant difference between transapical TAVI and SAVR at 12 months' follow-up.

In the transfemoral TAVI/SAVR subcohort, SF-12 physical and SF-12 mental scores were in favour of transfemoral TAVI at 1 month (*P* = .04 and *P* < .001, respectively), but there was no significant difference between the groups at 6 or 12 months. In the transapical TAVI/SAVR subcohort, the SF-12 mental score was in favour of SAVR at 1 month (*P* = .02) and the SF-12 physical score was in favour of SAVR at 6 months (*P* = .05). There was no difference between the two groups at other time points.

Table 3 and Figure 5 show the mean changes from baseline in quality-of-life scores for TAVI and SAVR in the PARTNER A trial.

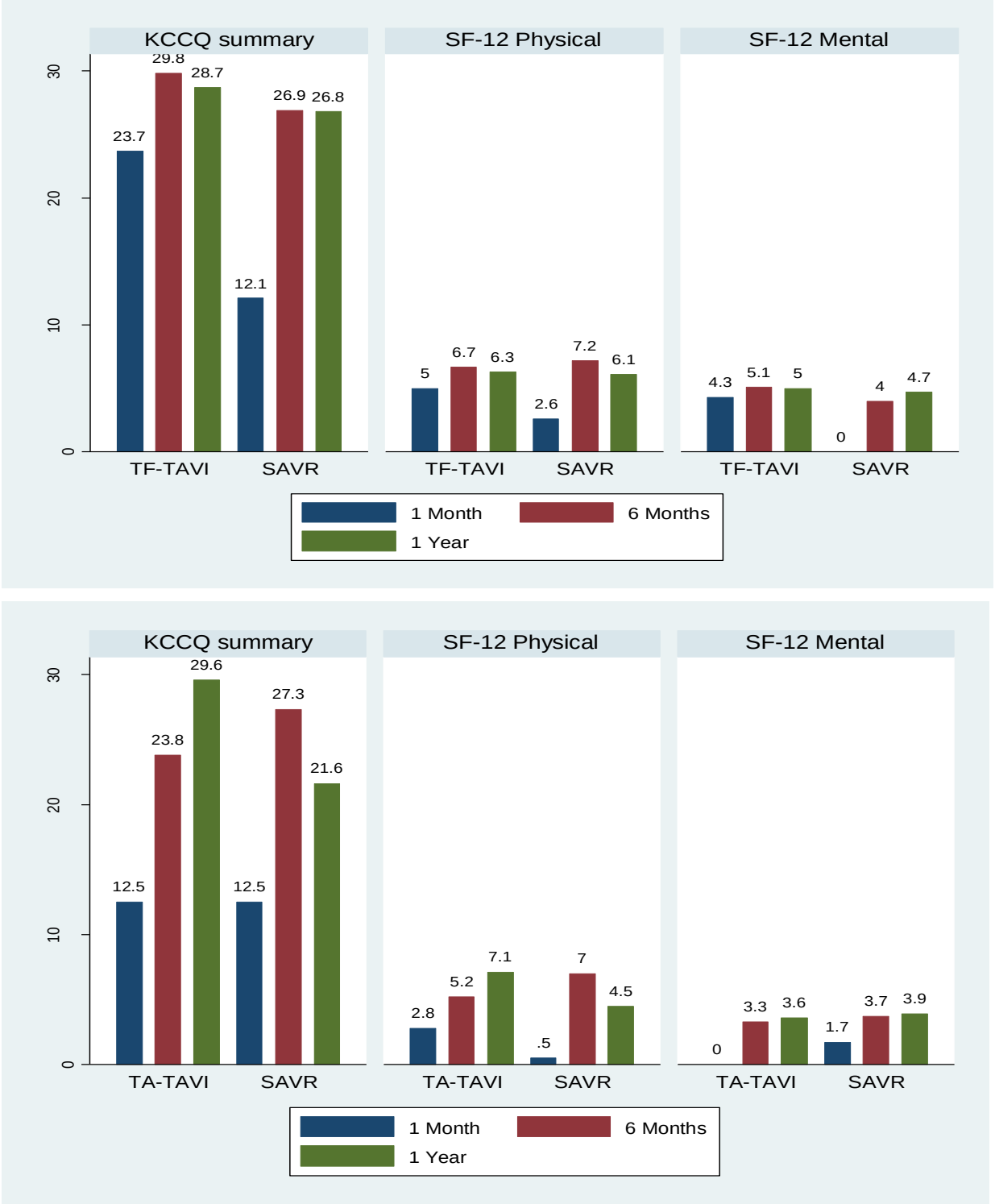

Figure 5: Mean Changes in Quality-of-Life Scores in PARTNER Trial Cohort A, TAVI (TF and TA) vs. SAVR[a]

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; SAVR, surgical aortic valve replacement; SF-12, 12-item Short Form questionnaire; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.

[a]Higher values indicate better improvement in health status.

Source: Data from Reynolds et al.[30]

In the US CoreValve trial,[21] 84% of patients were eligible for transfemoral TAVI, and 16% required nontransfemoral TAVI, which was performed either via the subclavian artery or using a direct aortic approach. Patients who underwent nontransfemoral TAVI had more cardiac comorbidities and peripheral vascular disease than those who underwent transfemoral TAVI. Overall, the mean KCCQ summary score was 46.8 points, which is generally consistent with NYHA functional class III. Baseline questionnaires were administered in person before the procedure, and follow-up questionnaires were administered by mail. Questionnaires that were not returned by mail in a timely fashion were administered by telephone interview. Health status data were available for 709 of 795 patients (89%) at baseline, and patients with missing baseline quality-of-life data were excluded from analysis. Data were available for 59%, 75%, and 74% of surviving patients at 1-month, 6-month, and 12-month follow-up.

Both disease-specific and generic scales showed substantial improvement at 1 year after either TAVI or SAVR and regardless of access site for TAVI. The comparison of quality-of-life scores between TAVI and SAVR, according to the longitudinal growth curve models, showed a significant interaction between treatment effect and access site at 1 month, so the authors reported the results separately for transfemoral TAVI and nontransfemoral TAVI. Patients who underwent transfemoral TAVI saw more rapid improvement in quality of life than those who underwent nontransfemoral TAVI or SAVR. The AMD between transfemoral TAVI and SAVR in KCCQ summary scores was 16.7 (95% CI, 12.0–21.3; $P < .001$) at 1 month, while for nontransfemoral TAVI, it was 3.6 (95% CI, –6.6 to 13.9; $P = .48$). At 6 and 12 months, there was no significant difference between TAVI and SAVR, regardless of access site.

The difference between transfemoral TAVI and SAVR in SF-12 physical and SF-12 mental scores was significant at 1 month in favour of transfemoral TAVI ($P < .001$ for both scales). At 6 months, SF-12 mental scores were still significantly better for transfemoral TAVI; SF-12 physical scores were better for SAVR, but the difference was not significant. The difference between nontransfemoral TAVI and SAVR in SF-12 physical and SF-12 mental scores was not significant at any time point.

Table 4 and Figures 6 and 7 show the mean changes from baseline in quality-of-life scores for TAVI and SAVR in the US CoreValve trial.

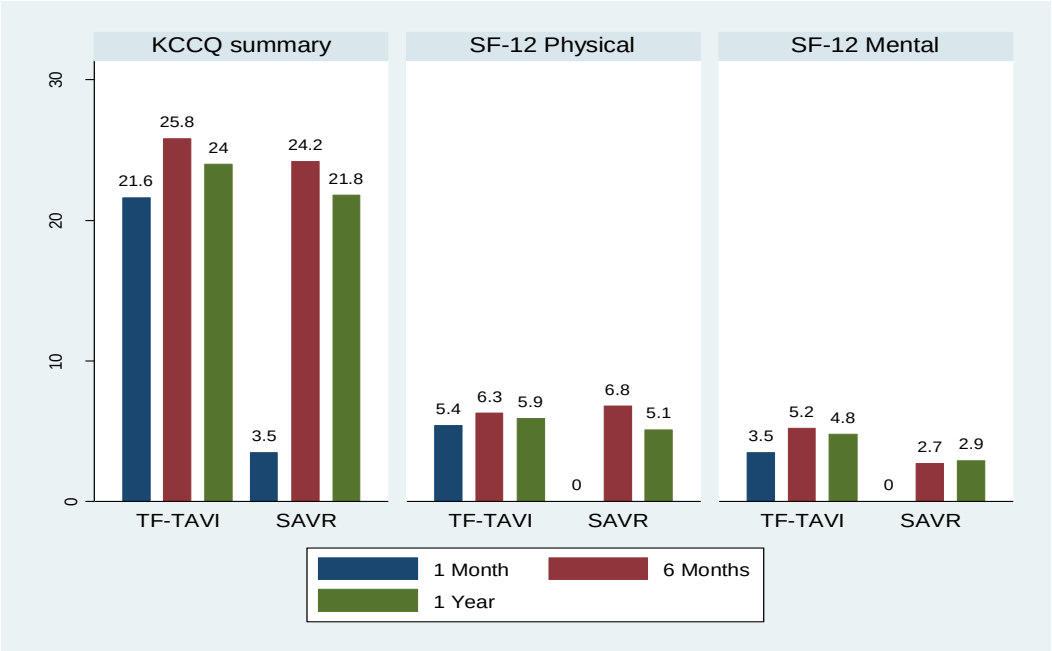

Figure 6: Mean Changes in Quality-of-Life Scores in the US CoreValve Trial, TF-TAVI vs. SAVR[a,b]

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; SAVR, surgical aortic valve replacement; SF-12, 12-item Short Form questionnaire; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
[a]Higher values indicate better improvement in health status.
[b]Changes in scores were paired differences calculated by the authors using paired Student's t-test.
Source: Data from Arnold et al.[33]

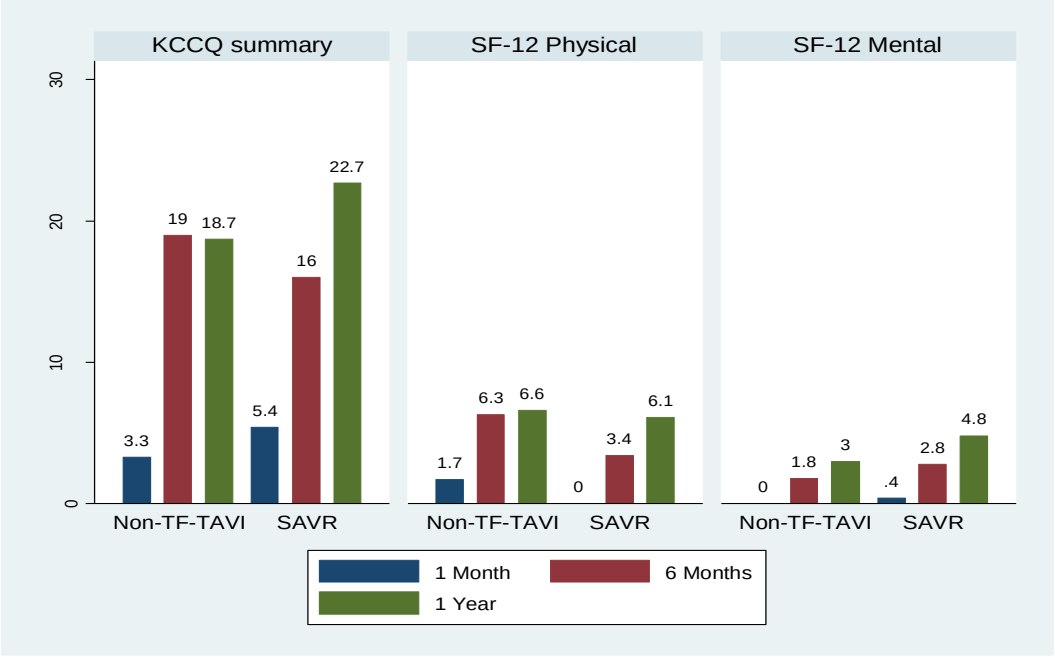

Figure 7: Mean Changes in Quality-of-Life Scores in the US CoreValve Trial, Non-TF-TAVI vs. SAVR[a,b]

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; SAVR, surgical aortic valve replacement; SF-12, 12-item Short Form questionnaire; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
[a]Higher values indicate better improvement in health status.
[b]Changes in scores were paired differences calculated by the authors using paired Student's t-test.
Source: Data from Arnold et al.[33]

Patients Who Were Not Suitable Candidates for Surgical Valve Replacement

In PARTNER trial cohort B,[19] which included high-risk patients who were not suitable candidates for surgical valve replacement, patients received either transfemoral TAVI or BAV. From 358 patients in the study, 327 (91%) completed a baseline questionnaire. Follow-up questionnaires at each time point were obtained from more than 80% of patients who survived. Given the high mortality rate among patients in this trial, 12-month quality-of-life outcome measures were available for only 61% of patients originally randomized to TAVI and 39% of patients randomized to BAV. The difference between transfemoral TAVI and BAV at each time point was estimated from longitudinal random-effect growth curve models that used all available quality-of-life data, including data from patients who subsequently died, withdrew, or were lost to follow-up.

The mean KCCQ summary scores improved over time in both the transfemoral TAVI and BAV groups. For transfemoral TAVI, the mean change from baseline in KCCQ summary scores was 25 points at 1 month, 34 points at 6 months, and 32 points at 12 months ($P < .001$ for all comparisons). For the BAV group, the mean change from baseline in KCCQ summary scores was 10 points at 1 month and 12 points at 6 months ($P < .001$ for both comparisons) but only 4 points at 12 months ($P = .2$). A similar pattern was seen for KCCQ subscales and the SF-12 summary scale.

The difference between transfemoral TAVI and BAV for KCCQ summary scores, based on longitudinal growth curve models, was significant at all time points in favour of transfemoral TAVI (at 1 month: 13.3 points; 95% CI, 7.6–19; $P < .001$ / at 6 months: 20.8 points; 95% CI, 14.7–27; $P < .001$ / at 12 months: 26.0 points; 95% CI, 18.7–33.3; $P < .001$).

The difference between transfemoral TAVI and BAV in SF-12 physical and SF-12 mental scores was also significant at all time points except for the SF-12 mental score at 1 month, which did not show any differences between the two groups.

Table 6 and Figure 8 show mean changes from baseline in quality-of-life scores for transfemoral TAVI and BAV in high-risk patients who were not suitable candidates for surgery.

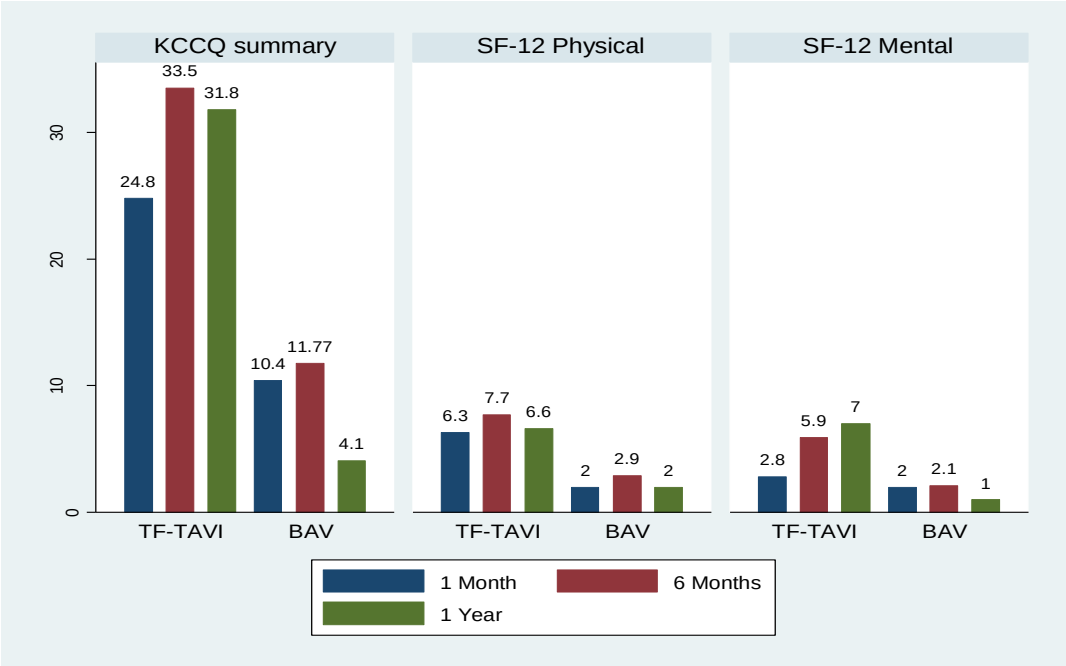

Figure 8: Mean Changes in Quality-of-Life Scores for Patients Who Were Not Suitable Candidates for Cardiac Surgery, TAVI vs. BAV[a]

Abbreviations: BAV, balloon aortic valvuloplasty; KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-12, 12-item Short Form questionnaire; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
[a]Higher values indicate better improvement in health status.
Source: Data from Reynolds et al.[24]

Results for Safety

Tables 8 to 11 show the major adverse events in both arms of the TAVI trials. For this review, we focused on outcomes that were different between the two techniques. Rates of myocardial infarction were not different between TAVI and SAVR in any trial. Rates of renal failure were different across studies. The PARTNER trial cohort A[20] reported no difference between TAVI and SAVR for rate of renal failure requiring dialysis. In the trial of low-risk patients using the SAPIEN valve,[23] the rate of renal failure requiring dialysis was 2.9% in the transapical TAVI group and 0% in SAVR group. The US CoreValve trial[21] reported higher rates of acute kidney injury, but the definition of this outcome was not reported.

The GRADE evidence profile for safety is presented in Table 12.

Table 8: Adverse Outcomes After TAVI or SAVR in PARTNER Trial, Cohort A, Intention-to-Treat Analysis[a]

Author, Year	All-Cause Mortality, N (%)	Cardiovascular Mortality, N (%)	Aortic Regurgitation, N (%)		Stroke, N (%)	Vascular Complications, N (%)	Major Bleeding, N (%)	New Pacemaker, N (%)	Myocardial Infarction, N (%)	Renal Failure, N (%)
			Paravalvular	Transvalvular						
30 days Smith et al, 2011[20]	TAVI: 12 (3.4) SAVR: 22 (6.5) *P* = .07	TAVI: 11 (3.2) SAVR: 10 (3.0) *P* = .90	**Moderate/severe** TAVI: 35/287 (12.2) SAVR: 2/229 (0.9) **Mild** TAVI: 187/287 (65.2) SAVR: 58/229 (25.3)	**Moderate/severe** TAVI: 3/291 (0.1) SAVR: 2/230 (0.9) **Mild** TAVI: 185/291 (63.6) SAVR: 100/230 (43.2)	**Major** TAVI: 13 (3.8) SAVR: 7 (2.1) *P* = .20 **Minor** TAVI: 3 (0.9) SAVR: 1 (0.3) *P* = .34	**All** TAVI: 59 (17) SAVR: 13 (3.8) *P* < .001 **Major** TAVI: 38 (11.0) SAVR: 11 (3.2) *P* < .001	TAVI: 32 (9.3) SAVR: 67 (19.5) *P* < .001	TAVI: 13 (3.8) SAVR: 12 (3.6) *P* = .89	TAVI: 0 (0) SAVR: 2 (0.6) *P* = .16	TAVI: 10 (2.9) SAVR: 10 (3.0) *P* = .95
1 year Smith et al, 2011[20]	TAVI: 84 (24.2) SAVR: 89 (26.8) *P* = .44	TAVI: 47 (14.3) SAVR: 40 (13) *P* = .63	**Moderate/severe** TAVI: 15/222 (6.8) SAVR: 3/159 (1.9) *P* < .001 **Mild** TAVI: 134/222 (60.4) SAVR: 32/159 (20.1)	**Moderate/severe** TAVI: 2/225 (0.9) SAVR: 0/159 (0) **Mild** TAVI: 141/225 (62.7) SAVR: 71/159 (44.7)	**Major** TAVI: 17 (5.1) SAVR: 8 (2.4) *P* = .07 **Minor** TAVI: 3 (0.9) SAVR: 2 (0.7) *P* = .84	**All** TAVI: 62 (18) SAVR: 16 (4.8) *P* < .001 **Major** TAVI: 39 (11.3) SAVR: 12 (3.5) *P* < .001	TAVI: 49 (14.7) SAVR: 85 (25.7) *P* < .001	TAVI: 19 (5.7) SAVR: 16 (5.0) *P* = .68	TAVI: 1 (0.4) SAVR: 2 (0.6) *P* = .69	TAVI: 18 (5.4) SAVR: 20 (6.5) *P* = .56
2 years Kodali et al, 2012[12] Miller et al, 2012[29]	TAVI: 116 (33.9) SAVR: 114 (35) *P* = .78	TAVI: 67 (21.4) SAVR: 59 (20.5) *P* = .8	**Moderate/severe** TAVI: (6.9) SAVR: (0.9) *P* < .001 **Mild** TAVI: (38.6) SAVR: (6.3)	NA	**Major** TAVI: 18 (5.2) SAVR: 10 (2.8) **Minor** TAVI: 5 (1.5) SAVR: 1 (0.3)	TAVI: 40 (11.6) SAVR: 13 (3.8) *P* < .001	TAVI: 60 (19.0) SAVR: 95 (29.5) *P* = .002	TAVI: 23 (7.2) SAVR: 19 (6.4) *P* = .69	TAVI: 0 (0) SAVR: 4 (1.5) *P* = .05	TAVI: 20 (6.2) SAVR: 21 (6.9) *P* = .75
5 years Mack et al, 2015[32]	TAVI: 229 (67.8) SAVR: 198 (62.4) *P* = .76	TAVI: 147 (53.1) SAVR: 123 (47.6) *P* = .67	TAVI: 85/100 (85.0) SAVR: 79/97 (81.4)	**Moderate/severe** TAVI: 2/280 (0.7) SAVR: 1/228 (0.4) **Mild** NA	TAVI: 29 (10.4) SAVR: 26 (11.3) *P* = .61	TAVI: 41 (11.9) SAVR: 14 (4.7) *P* = .0002	TAVI: 75 (26.6) SAVR: 103 (34.4) *P* = .003	TAVI: 28 (9.7) SAVR: 23 (9.1) *P* = .64	TAVI: 5 (2.9) SAVR: 11 (5.9) *P* = .15	TAVI: 24 (8.6) SAVR: 24 (8.5) *P* = .69

Abbreviations: NA, not available; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]Percentages are based on Kaplan-Meier estimates as reported by the authors and do not equal the number of patients with events divided by the total number of patients.

Table 9: Adverse Outcomes After TAVI or SAVR in US CoreValve Trial, As-Treated Analysis[a]

Author, Year	All-Cause Mortality, N (%)	Cardiovascular Mortality, N (%)	Paravalvular Aortic Regurgitation, N (%)	Stroke, N (%)	Major Vascular Complications, N (%)	Major Bleeding, N (%)	New Pacemaker, N (%)	Myocardial Infarction, N (%)	Renal Failure, N (%)
30 days Adams et al, 2014[21]	TAVI: 13 (3.3) SAVR: 16 (4.5) *P* = .43	TAVI: 12 (3.1) SAVR: 16 (4.5) *P* = .32	**Moderate/severe** TAVI: 32 (9.0) SAVR: 3 (1.0) *P* < .001 **Mild** TAVI: 127 (35.7) SAVR: 10 (3.3)	**Major** TAVI: 15 (3.9) SAVR: 11 (3.1) *P* = .55 **Minor** TAVI: 4 (1.0) SAVR: 12 (3.4) *P* = .03	TAVI: 23 (5.9) SAVR: 6 (1.7) *P* = .003	TAVI: 109 (28.1) SAVR: 123 (34.5) *P* = .05	TAVI: 76 (19.8) SAVR: 25 (7.1) *P* < .001	TAVI: 3 (0.8) SAVR: 3 (0.8) *P* = .92	TAVI: 23 (6.0) SAVR: 54 (15.1) *P* < .001
1 year Adams et al, 2014[21]	TAVI: 55 (14.2) SAVR: 67 (19.1) *P* = .04	TAVI: 40 (10.4) SAVR: 44 (12.8) *P* = .31	**Moderate/severe** TAVI: 18 (6.1) SAVR: 1 (0.5) *P* < .001 **Mild** TAVI: 76 (25.8) SAVR: 10 (4.5)	**Major** TAVI: 22 (5.8) SAVR: 23 (7.0) *P* = .59 **Minor** TAVI: 11 (3.0) SAVR: 20 (6.0) *P* = .05	TAVI: 24 (6.2) SAVR: 7 (2.0) *P* = .004	TAVI: 114 (29.5) SAVR: 130 (36.7) *P* = .03	TAVI: 85 (22.3) SAVR: 38 (11.3) *P* < .001	TAVI: 7 (1.9) SAVR: 5 (1.5) *P* = .70	TAVI: 23 (6.0) SAVR: 54 (15.1) *P* < .001
2 years Reardon et al, 2015[34]	TAVI: 85 (22.2) SAVR: 99 (28.6) *P* = .04	TAVI: 58 (15.4) SAVR: 64 (19.4) *P* = .19	**Moderate/severe** TAVI: 15 (6.1) SAVR: 1 (0.6) *P* < .001 **Mild** TAVI: 73 (29.9) SAVR: 13 (7.2)	**Major** TAVI: 25 (6.8) SAVR: 30 (9.8) *P* = .25 **Minor** TAVI: 15 (4.2) SAVR: 23 (7.3) *P* = .08	TAVI: 27 (7.1) SAVR: 7 (2.0) *P* = .001	TAVI: 123 (32.3) SAVR: 135 (38.2) *P* = .07	TAVI: 96 (25.8) SAVR: 42 (12.8) *P* < .001	TAVI: 7 (1.9) SAVR: 7 (2.3) *P* = .83	TAVI: 24 (6.2) SAVR: 54 (15.1) *P* < .001

Abbreviations: NA, not available; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]Percentages are based on Kaplan-Meier estimates as reported by the authors and do not equal the number of patients with events divided by the total number of patients.

Table 10: Adverse Outcomes After TAVI or SAVR in Low-Risk Patients: As-Treated Analysis

Author, Year	All-Cause Mortality, N (%)	Cardiovascular Mortality, N (%)	Paravalvular Aortic Regurgitation, N (%)	Stroke, N (%)	Major Vascular Complications, N (%)	Major Bleeding, N (%)	Permanent Pacemaker, N (%)	Myocardial Infarction, N (%)	Renal Failure, N (%)
NOTION Trial (TF TAVI)									
30 days Thyregod et al, 2015[22]	TAVI: 3 (2.1) SAVR: 5 (3.7) *P* = .43	TAVI: 3 (2.1) SAVR: 5 (3.7) *P* = .43	NA	TAVI: 2 (1.4) SAVR: 4 (3.0) *P* = .37	TAVI: 8 (5.6) SAVR: 2 (1.5) *P* = .10	TAVI: 16 (11.3) SAVR: 28 (20.9) *P* = .03	TAVI: 46 (34.1) SAVR: 2 (1.6) *P* < .001	TAVI: 4 (2.8) SAVR: 8 (6.0) *P* = .20	TAVI: 1 (0.7) SAVR: 9 (6.7) *P* = .01
1 year Thyregod et al, 2015[22]	TAVI: 7 (4.9) SAVR: 10 (7.5) *P* = .38	TAVI: 6 (4.3) SAVR: 10 (7.5) *P* = .25	NA	TAVI: 4 (2.9) SAVR: 6 (4.6) *P* = .44	NA	NA	TAVI: 51 (38) SAVR: 3 (2.4) *P* < .001	TAVI: 5 (3.5) SAVR: 8 (6.0) *P* = .33	NA
STACCATO Trial (TA TAVI)									
30 days Nielsen et al, 2012[23]	TAVI: 1 (2.9) SAVR: 0 (0)	TAVI: 1 (2.9) SAVR: 0 (0)	NA	TAVI: 2 (5.9) SAVR: 1 (2.8)	TAVI: 1 (2.9) SAVR: 0 (0)	TAVI: 1 (2.9) SAVR: 1 (2.8)	TAVI: 2 (5.9) SAVR: 1 (2.8)	TAVI: 0 (0) SAVR: 0 (0)	TAVI: 1 (2.9) SAVR: (0)
3 months Nielsen et al, 2012[23]	TAVI: 4 (11.8) SAVR: 0 (0)	TAVI: 3 (8.8) SAVR: 0 (0)	**Severe** TAVI: 2 (5.9) SAVR: 0 (0) **Mild** TAVI: 2 (5.9) SAVR: 0 (0)	TAVI: 3 (8.8) SAVR: 1 (2.8)	NA	NA	TAVI: 2 (5.9) SAVR: 1 (2.8)	TAVI: 0 (0) SAVR: 0 (0)	TAVI: 1 (2.9) SAVR: 0 (0)

Abbreviations: NA, not available; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.

Table 11: Adverse Outcomes After TAVI or BAV in Patients Who Were Not Suitable Candidates for Surgery: Intention-to-Treat Analysis[a]

Author, Year	All-Cause Mortality, N (%)	Cardiovascular Mortality, N (%)	Aortic Regurgitation, N (%)		Stroke, N (%)	Vascular Complications, N (%)	Major Bleeding, N (%)	New Pacemaker, N (%)	Myocardial Infarction, N (%)	Renal Failure, N (%)
			Paravalvular	Transvalvular						
30 days Leon et al, 2010[19]	TAVI: 9 (5.0) BAV: 5 (2.8) *P* = .41	TAVI: 8 (4.5) BAV: 3 (1.7) *P* = .22	**Moderate/severe** TAVI: 17/141 (12.1) BAV: 0 (0) **Mild** TAVI: 74/141 (52.5) BAV: 0 (0)	**Moderate/severe** TAVI: 2/141 (1.3) BAV: 24/141 (16.9)	**Major** TAVI: 9 (5.0) BAV: 2 (1.1) *P* = .06 **Minor** TAVI: 3 (1.7) BAV: 1 (0.6) *P* = .62	**All** TAVI: 55 (30.7) BAV: 9 (5.0) *P* < .001 **Major** TAVI: 29 (16.2) BAV: 2 (1.1) *P* < .001	TAVI: 30 (16.8) BAV: 7 (3.9) *P* < .001	TAVI: 6 (3.4) BAV: 9 (5.0) *P* = .60	TAVI: 0 (0) BAV: 0 (0)	TAVI: 2 (1.1) BAV: 3 (1.7) *P* = 1.0
1 year Leon et al, 2010[19]	TAVI: 55 (30.7) BAV: 89 (49.7) *P* < .001	TAVI: 35 (19.6) BAV: 75 (41.9) *P* < .001	**Moderate/severe** TAVI: 7/89 (7.9) BAV: 0 (0) **Mild** TAVI: 40/89 (44.9) BAV: 0 (0)	**Moderate/severe** TAVI: 14/89 (15.7) BAV: 8/47 (17) **Mild** TAVI: 17/89 (19.1) BAV: 18/47 (38.3)	**Major** TAVI: 14 (7.8) BAV: 7 (3.9) *P* = .18 **Minor** TAVI: 4 (2.2) BAV: 1 (0.6) *P* = .37	**All** TAVI: 58 (32.4) BAV: 13 (7.3) *P* < .001 **Major** TAVI: 30 (16.8) BAV: 4 (2.2) *P* < .001	TAVI: 40 (22.3) BAV: 20 (11.2) *P* = .007	TAVI: 8 (4.5) BAV: 14 (7.8) *P* = .27	TAVI: 1 (0.6) BAV: 1 (0.6) *P* = 1.0	TAVI: 3 (1.7) BAV: 6 (3.4) *P* = .50
2 years Makkar et al, 2012[13]	TAVI: 77 (43.3) BAV: 117 (68.0) *P* < .001	TAVI: 50 (31.0) BAV: 100 (62.4) *P* < .001	**Moderate/severe** TAVI: 3/67 (4.5) BAV: 0 (0) **Mild** TAVI: 24/67 (35.8) BAV: 1/2 (50.0)	**Moderate/severe** TAVI: 2/67 (3.0) BAV: 3/23 (13) **Mild** TAVI: 11/67 (16.4) BAV: 10/23 (43.5)	**Major** TAVI: 18 (10.1) BAV: 7 (3.9) **Minor** TAVI: 4 (2.2) BAV: 1 (0.6)	NA	TAVI: 48 (28.9) BAV: 25 (20.1) *P* = .09	TAVI: 10 (6.4) BAV: 14 (8.6) *P* = .47	TAVI: 2 (1.6) BAV: 2 (2.5) *P* = .69	TAVI: 5 (3.2) BAV: 9 (7.6) *P* = .15
3 years Kapadia et al, 2014[25]	TAVI: NA (54.1) BAV: NA (80.9) *P* < .0001	TAVI: NA (41.4) BAV: NA (74.5) *P* < .0001	**Moderate/severe** TAVI: 2/44 (4.5) BAV: NA **Mild** TAVI: 14/44 (31.8) BAV: NA	NA	TAVI: NA (15.7) BAV: NA (5.5) *P* = .004	**Major** TAVI: NA (17.4) BAV: NA (2.8) *P* < .0001	TAVI: NA (32.0) BAV: NA (32.9) *P* = .92	TAVI: NA (7.6) BAV: NA (8.6) *P* = .75	TAVI: NA (4.1) BAV: NA (2.5) *P* = .59	TAVI: NA (3.2) BAV: NA (11.1) *P* = .08
5 years Kapadia et al, 2015[28]	TAVI: 130 (71.8) BAV: 174 (93.6) *P* < .0001	TAVI: (57.5) BAV: (85.9) *P* < .0001	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: BAV, balloon aortic valvuloplasty; NA, not available; TAVI, transcatheter aortic valve implantation.

[a]Percentages are based on Kaplan-Meier estimates as reported by the authors and do not equal the number of patients with events divided by the total number of patients.

Table 12: GRADE Evidence Profile for Safety, Comparison of TAVI and SAVR

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Mortality							
4 (RCTs)	No serious limitations	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Paravalvular Aortic Regurgitation							
4 (RCTs)	No serious limitations	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Major Stroke							
4 (RCTs)	No serious limitations	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Major Vascular Complications							
4 (RCTs)	No serious limitations	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Major Bleeding							
4 (RCTs)	No serious limitations	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Need for Pacemaker Implantation							
4 (RCTs)	No serious limitations	Undetermined	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

The results of the TAVI trials showed that major adverse events after TAVI procedures depend on patients' surgical risk. Comparison of cardiovascular mortality and major vascular complications in trials of patients from different risk categories showed that rates decreased as STS scores decreased (Figure 9). For stroke, the US CoreValve trial showed relatively higher rates of stroke than the other trials.[21]

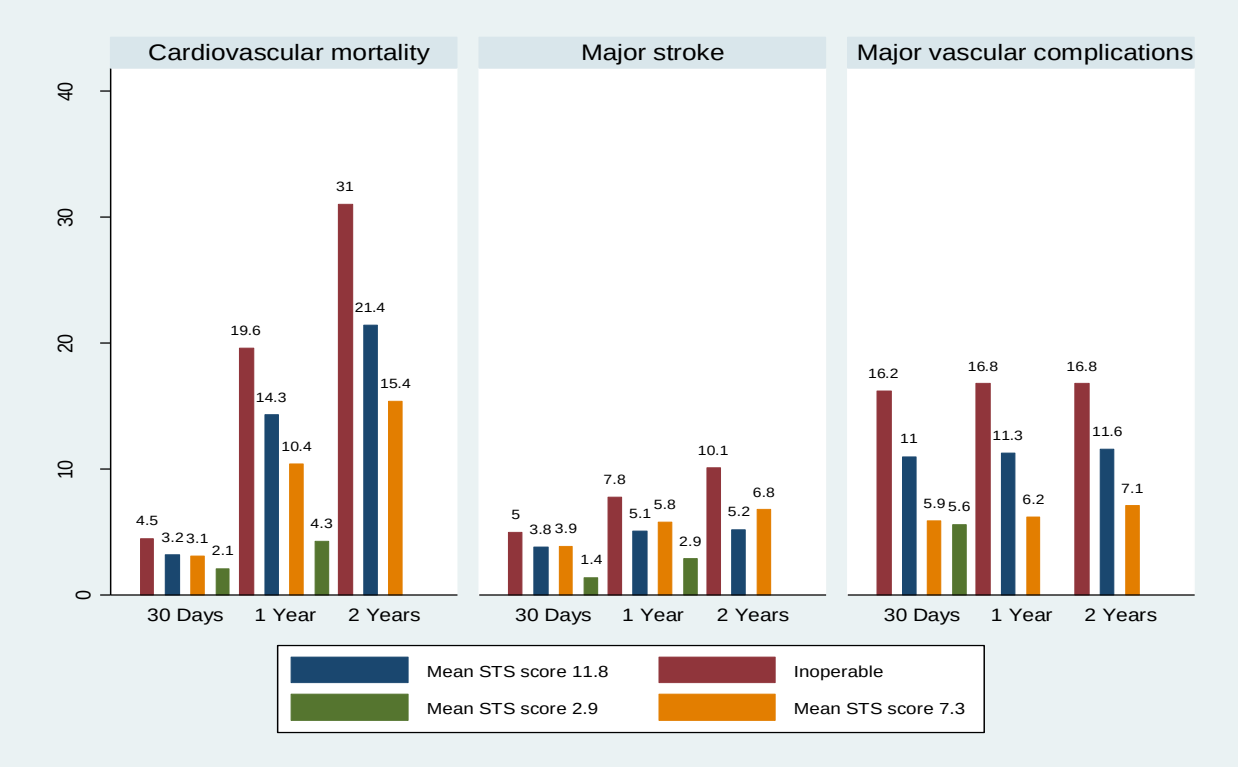

Figure 9: Two-Year Major Events in Transfemoral TAVI for Categories of Surgical Risk

Abbreviation: STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
Sources: Data from Leon et al,[19] Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] Mack et al,[32] Reardon et al.[34]

As well as patient risk category, the method of valve implantation also influenced outcomes. In PARTNER cohort A,[20] cardiovascular mortality and major stroke were both lower in patients who had transfemoral TAVI than in those who had transapical TAVI. On the other hand, major vascular complications were more frequent with transfemoral TAVI than transapical TAVI (Figure 10).

However, the difference between transfemoral TAVI and transapical TAVI may not depend only on the method of valve implantation, since the transapical cohort had increased rates of coexisting disorders before the procedure.[20] High-risk patients who underwent transapical TAVI were a subgroup of patients in cohort A of the PARTNER trial who were deemed not eligible for transfemoral TAVI and were therefore assigned to transapical TAVI. Overall, patients in both arms of the transapical subcohort had higher rates of peripheral vascular disease, cerebrovascular disease, atrial fibrillation, prior coronary artery bypass graft surgery, myocardial infarction, and calcified aorta.

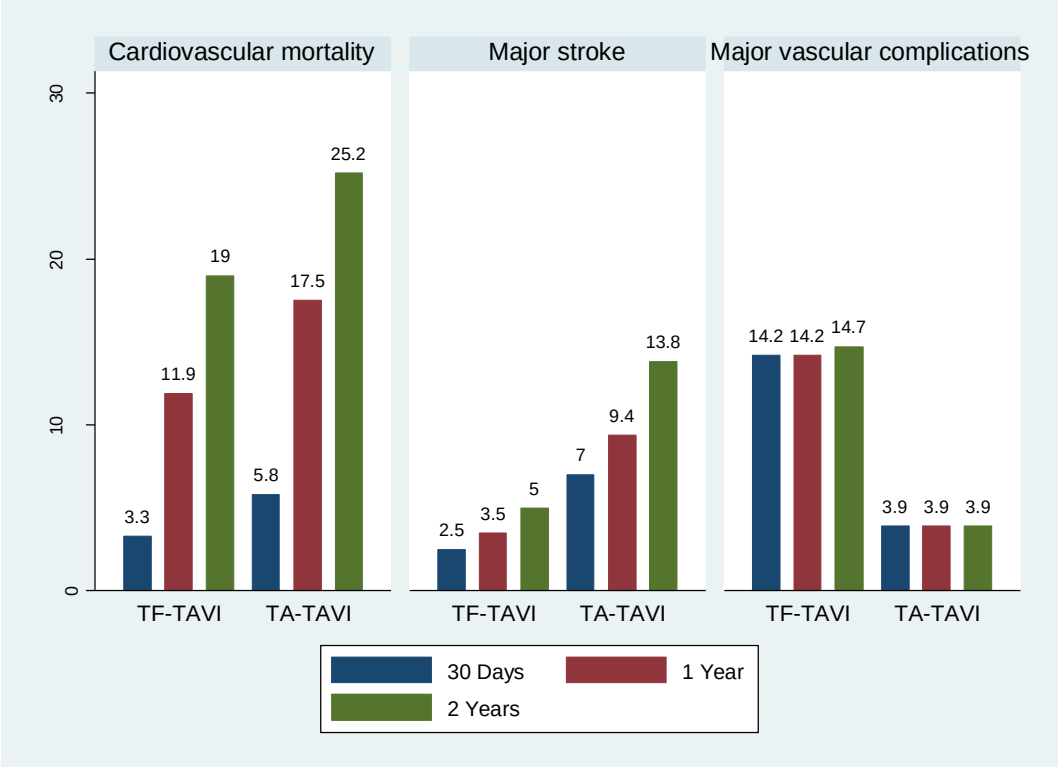

Figure 10: Two-Year Major Events for Transfemoral and Transapical TAVI in PARTNER Trial Cohort A

Abbreviations: TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
Sources: Data from Smith et al[20] and Kodali et al.[12]

In a trial of low-risk patients,[23] transapical TAVI performed poorly compared to SAVR. The trial was terminated prematurely due to frequent occurrence of adverse events in the transapical TAVI group. The primary outcome of this study was a composite of 30-day all-cause mortality, major stroke, and renal failure requiring dialysis. Among 34 patients who underwent transapical TAVI, five (14.7%) met the criteria for the primary end point within 30 days. Among 36 patients in the SAVR group, only 1 (2.8%) had a major stroke and fulfilled the primary end point. At 3 months, there were four deaths, three patients with stroke, and one patient with renal failure (total of eight [23.5%]) in the transapical TAVI group, whereas no death or renal failure and no additional major stroke occurred in the SAVR group (Figure 11).

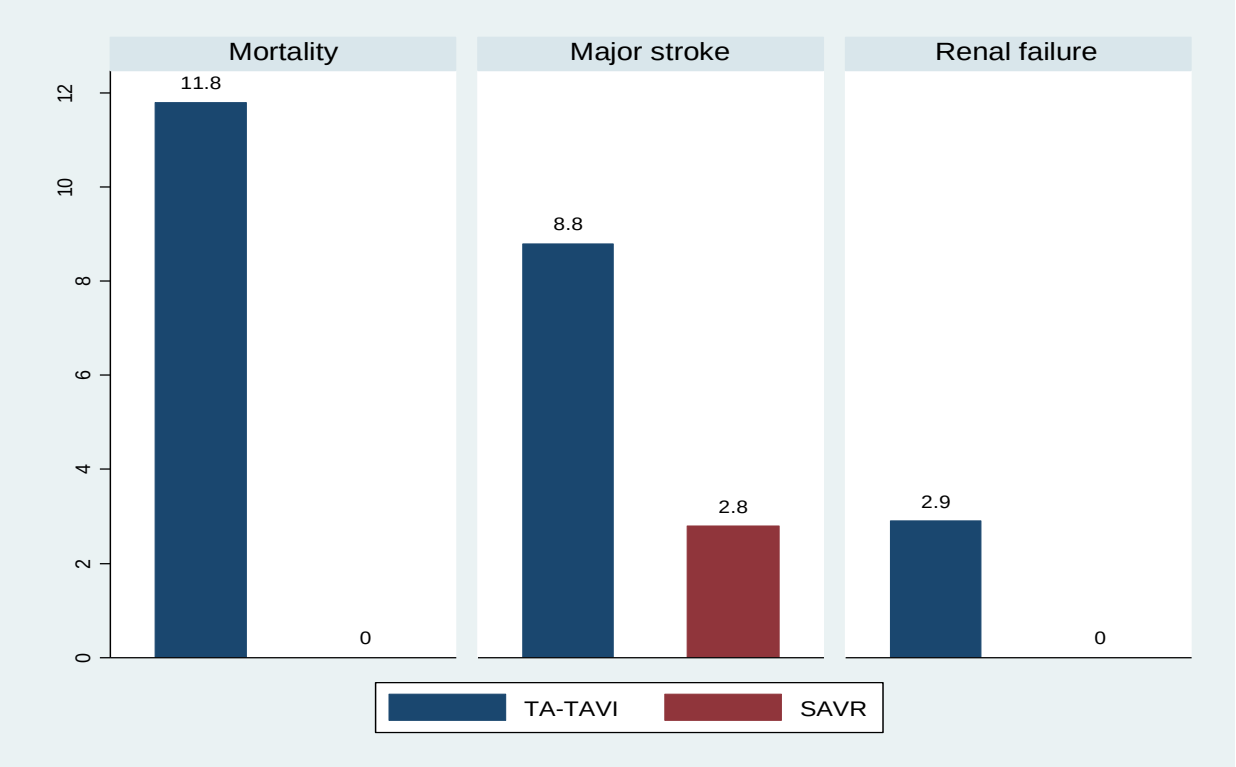

Figure 11: Three-Month Major Events for Transapical TAVI vs. SAVR in Low-Risk Patients

Abbreviations: SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation.
Source: Data from Nielsen et al.[23]

Mortality

Figures 12 and 13 show all-cause mortality and cardiovascular mortality in trials that compared TAVI with SAVR.

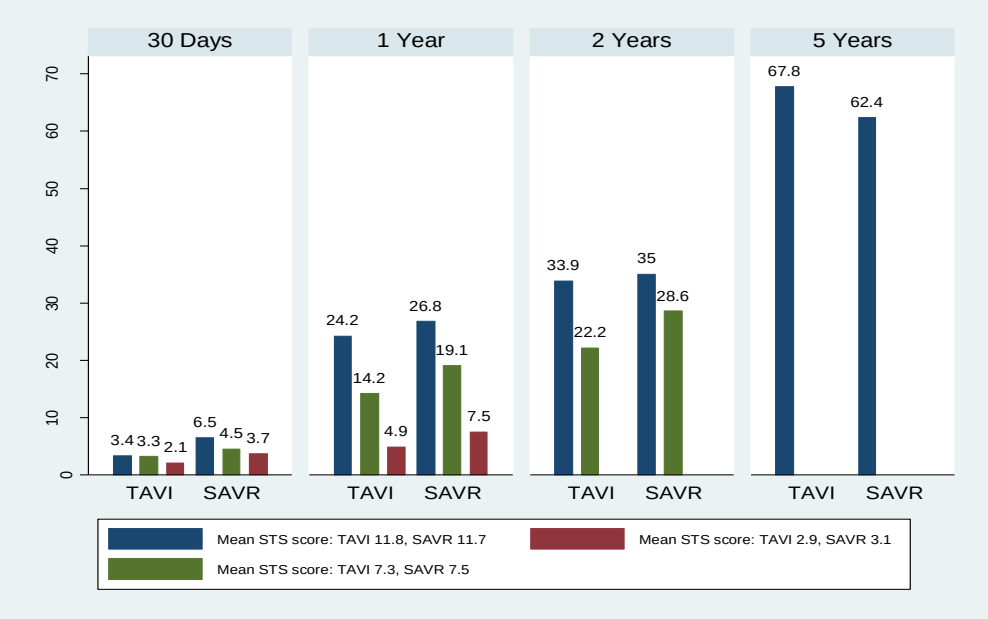

Figure 12: All-Cause Mortality by Category of Surgical Risk, TAVI vs. SAVR[a]

Abbreviations: SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
[a]High-risk based on intention-to-treat analysis; intermediate-risk and low-risk based on as-treated analysis.
Sources: Data from Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] Mack et al,[32] and Reardon et al.[34]

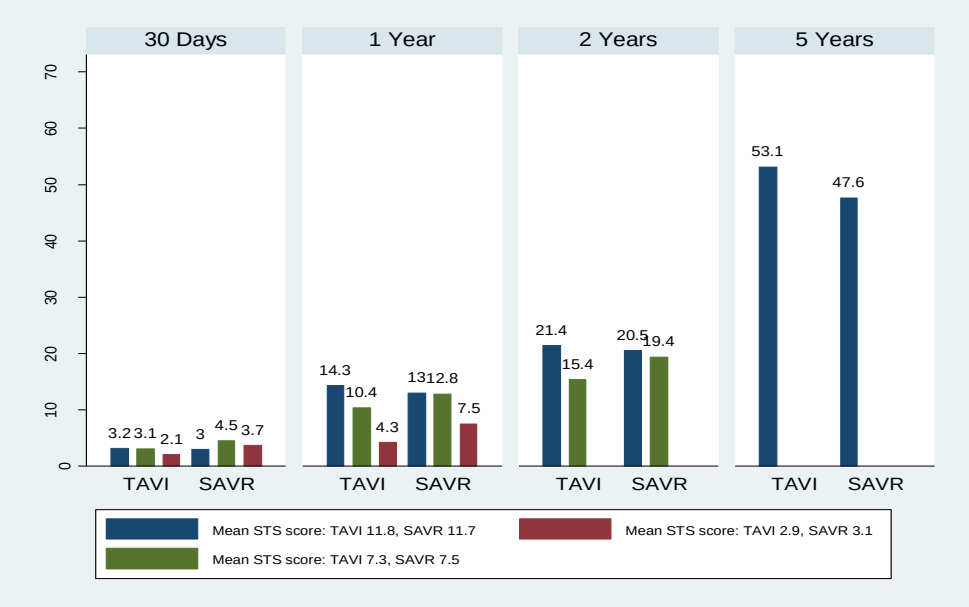

Figure 13: Cardiovascular Mortality by Category of Surgical Risk, TAVI vs. SAVR[a]

Abbreviations: SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
[a]High-risk based on intention-to-treat analysis; intermediate-risk and low-risk based on as-treated analysis.
Sources: Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] Mack et al,[32] and Reardon et al.[34]

In PARTNER trial cohort A,[20] in which patients underwent transfemoral or transapical TAVI, there was no statistically significant difference in all-cause or cardiovascular mortality between TAVI and SAVR at any time point and up to 5 years' follow-up.

In the US CoreValve trial,[21] patients in the TAVI arm underwent transarterial TAVI only. The as-treated population included 747 patients (390 TAVI and 357 SAVR). The majority of patients (83%) in the TAVI arm underwent transfemoral TAVI. The access route for the remaining TAVI patients (17%) was via the subclavian artery or the aorta. The results of this trial showed no significant difference in cardiovascular mortality between TAVI and SAVR up to 2 years' follow-up. However, all-cause mortality was significantly lower in TAVI at 1 and 2 years' follow-up (P = .04 at both time points).

In both trials, the predicted risk of death within 30 days for undergoing SAVR was overestimated. The observed mortality within 30 days was 6.5% in the PARTNER trial[20] and 4.5% in the CoreValve trial,[21] while the predicted mortality in the two trials were 11.7% and 7.5%, respectively.

In the NOTION trial,[22] the main route of access in the TAVI group was transfemoral (96.5%), and the subclavian artery was used as the entry site in the remaining TAVI patients. This trial found no significant difference in all-cause or cardiovascular mortality between the TAVI and SAVR groups up to 1 year of follow-up.

In a trial of patients who were not suitable candidates for surgery,[19] mortality was significantly lower in patients who received transfemoral TAVI than those who received BAV. Median survival was 31 months in the transfemoral TAVI group and 11.7 months in the BAV group (P < .0001). Cardiovascular mortality was higher in the transfemoral TAVI group in the first 30 days compared to BAV, but at 1 year and 2 years, it was about half that of the BAV group (Figure 14).

It appears that BAV was not helpful in improving the survival of patients with severe aortic valve stenosis: two-thirds of the patients in the BAV arm died due to cardiovascular causes in the first 2 years after randomization.[13] At 5-year follow-up, only six patients in BAV group were alive, of whom two had undergone TAVI, two had undergone SAVR, and one had undergone an aorta valve conduit. Only one patient among the survivors in the BAV arm had not had a valve replacement. The authors noted that it was difficult to analyze the effect of BAV in these patients, because it was done at the discretion of the investigators and was not part of the study protocol.

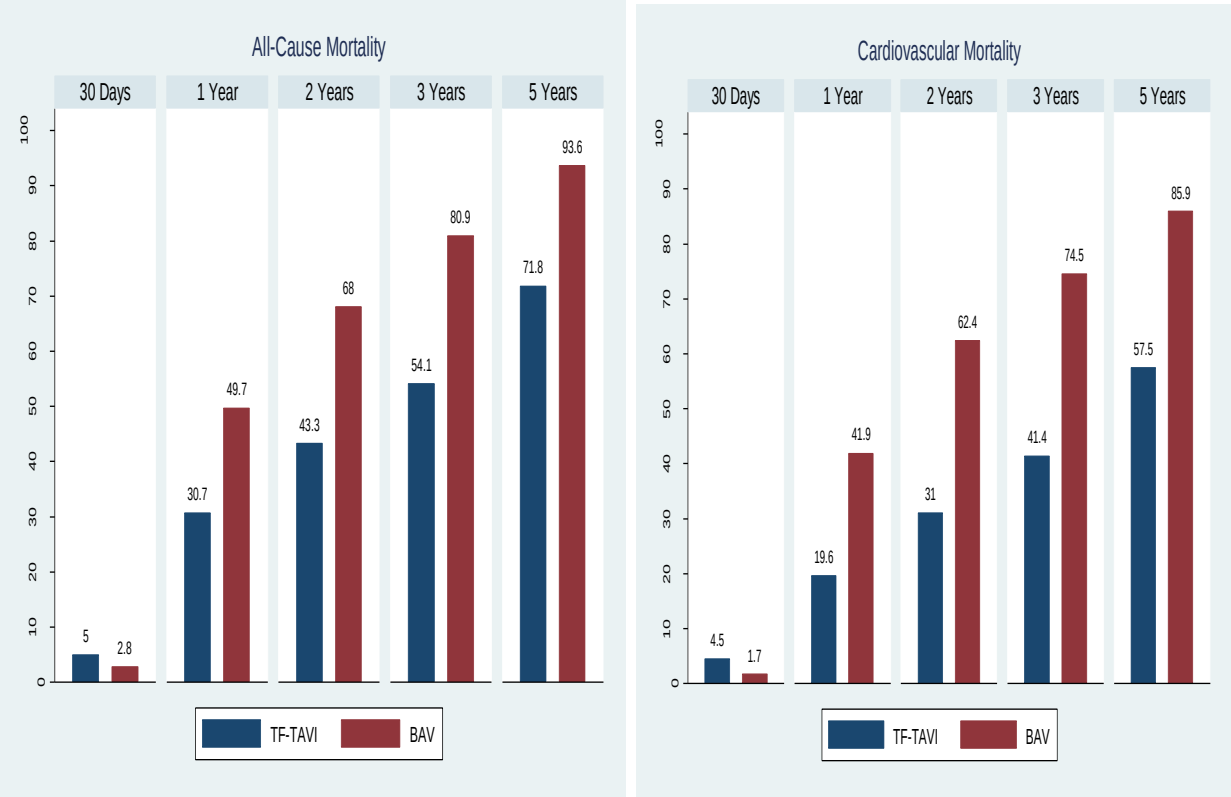

Figure 14: All-Cause and Cardiovascular Mortality, Transfemoral TAVI vs. BAV

Abbreviations: BAV, balloon aortic valvuloplasty; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
Sources: Data from Leon et al,[19] Makkar et al,[13] Kapadia et al,[25] and Kapadia et al.[28]

Causes of Death in Patients who Underwent TAVI

Svensson et al[26] have analyzed causes of death in cohorts A and B of the PARTNER trial, which included high-risk patients. The median follow-up was 2 years for cohort A, and 10% of survivors were followed for more than 3 years. The median follow-up for cohort B was 1.3 years, and 10% of survivors were followed for more than 3.2 years.

In both cohorts A and B, the most common cause of cardiovascular death in patients who underwent TAVI was heart failure (about 40% in the transfemoral TAVI or transapical TAVI arms of cohort A and 33% in the transfemoral TAVI arm of cohort B).

In the transfemoral TAVI arms of cohorts A and B, the other two most common causes of cardiovascular death were sudden death (27% in the transfemoral TAVI arm of cohort A and 10% in the transfemoral TAVI arm of cohort B) and stroke (15% in the transfemoral TAVI arm of cohort A and 18% in the transfemoral TAVI arm of cohort B).

In patients who underwent transapical TAVI in PARTNER trial cohort A, arrhythmia was the second most common cause of cardiovascular death after heart failure (30%). In patients who underwent transfemoral TAVI in both cohorts of the PARTNER trial, arrhythmia was responsible for only 2.5% to 3% of cardiovascular deaths.

Infection/sepsis was the most common noncardiovascular cause of death in both TAVI and SAVR groups of the PARTNER trial. Renal disease, malignancy, and respiratory problems were other competing causes of noncardiovascular death in both cohorts.

The rate of major stroke was considerably higher for transapical TAVI than for transfemoral TAVI at all time points (Figure 10). However, in transapical TAVI there was no death due to stroke, and in transfemoral TAVI about one-sixth of cardiovascular deaths were due to stroke (15% in cohort A and 18% in cohort B).

Causes of death in other trials were not reported.

Paravalvular Aortic Regurgitation

A troublesome adverse event after TAVI was the frequent occurrence of paravalvular aortic regurgitation. Moderate or severe paravalvular aortic regurgitation was significantly more common after TAVI than after SAVR in all trials and at all time points (Tables 4–7).

In PARTNER trial cohort A,[20] mild and moderate to severe paravalvular aortic regurgitation occurred in 65.2% and 12.2% of TAVI patients, respectively, during the first month. The presence of paravalvular aortic regurgitation after TAVI was also associated with increased late mortality in high-risk patients (hazard ratio, 2.11; 95% CI, 1.43–3.10; $P < .001$), and the effect was proportional to the severity of the regurgitation. However, even mild aortic regurgitation was associated with increased late mortality.[12]

In PARTNER trial cohort B (patients who were not suitable candidates for surgery), there was association between cardiac mortality and paravalvular aortic regurgitation. At 30 days, mild and moderate to severe paravalvular aortic regurgitation occurred in 52.5% and 12.1% of patients, respectively, who underwent transfemoral TAVI.[27] Analysis of data at 3 years demonstrated a modest trend toward a higher mortality in patients with moderate to severe and even mild paravalvular aortic regurgitation.[25]

In the US CoreValve trial, mild and moderate to severe paravalvular aortic regurgitation occurred in 35.7% and 9% of patients, respectively, at 30 days after the procedure, but it did not have an adverse effect on overall survival.[21]

The NOTION trial[22] reported only the rate of total aortic regurgitation. In this trial, the rate of moderate to severe total aortic regurgitation at 1 year was 15.7% in the transfemoral TAVI group and 0.9% in the SAVR group ($P < .001$), and this rate remained the same during the first year. The rate of moderate to severe total aortic regurgitation in the TAVI arm at 1 year in this trial was about twice that in the TAVI arm of the US CoreValve trial assessed at 1 year (7%).

Figure 15 shows the rates of mild and moderate to severe paravalvular aortic regurgitation among trials.

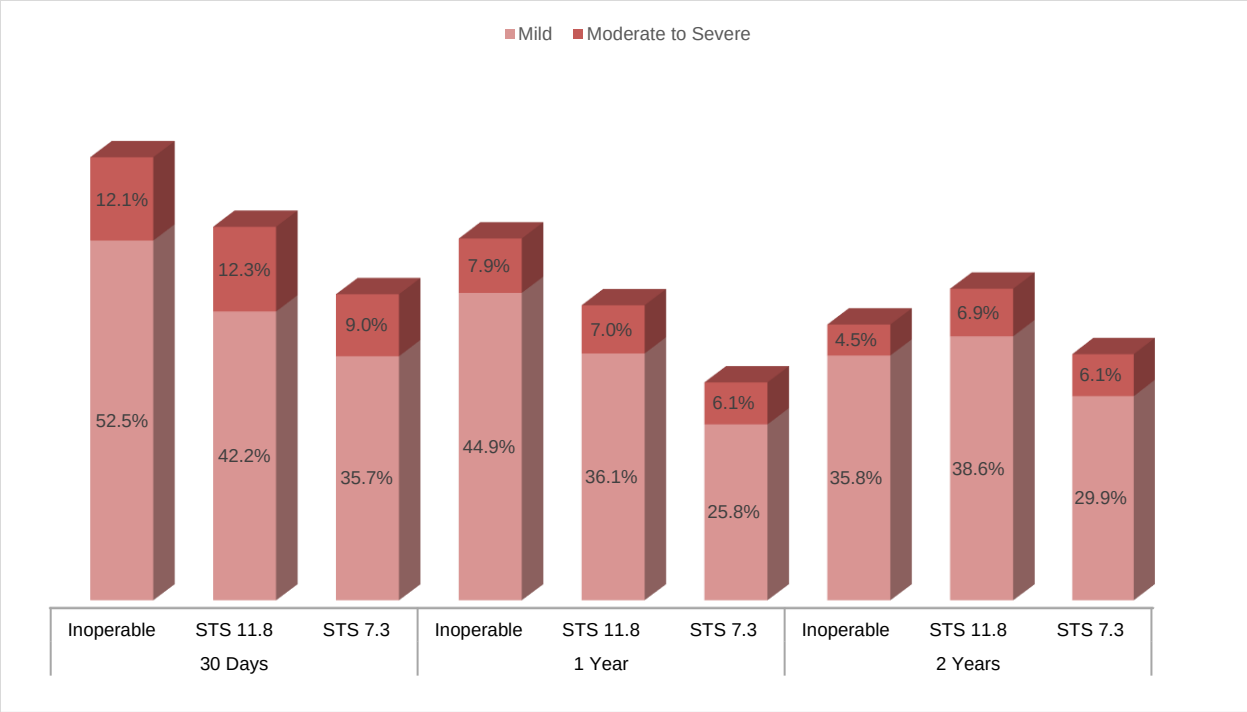

Figure 15: Paravalvular Aortic Regurgitation by Category of Surgical Risk, TAVI

Abbreviation: STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
Sources: Data from Douglas et al,[27] Adams et al,[21] Reardon et al,[34] and Hahn et al.[31]

Stroke

In PARTNER trial cohort A,[20] the combined rate of stroke and transient ischemic attack at 1 year was significantly higher in the TAVI group than in the SAVR group (8.3% vs. 4.3%: *P* = .04). The rate of major stroke in the TAVI group was about twice that of the SAVR group at 1 and 2 years, but it did not reach statistical significance—possibly because the study was not powered for this outcome.

In PARTNER trial cohort B (patients who were not suitable candidates for cardiac surgery),[19] the rate of stroke or transient ischemic attack was significantly higher in the transfemoral TAVI group than in the BAV group at 30 days (6.7% vs. 1.7%; *P* = .03) and at 1 year (10.6% vs. 4.5%, *P* = .04, respectively). The rate of major stroke at 30 days was five times higher in the transfemoral TAVI group than in the BAV group (5.0% vs. 1.1%; *P* = .06). The rate of major stroke in the transfemoral TAVI group was twice that for the BAV group at 1 year (7.8% vs. 3.9%; *P* = .18) and three times higher at 3 years (transfemoral TAVI, 15.7%; BAV, 5.5%; *P* = .004) (Figure 17).

The US CoreValve trial[21] showed a relatively higher rate of major stroke in both arms at 1- and 2-year follow-up compared to other trials. In contrast to the results of the PARTNER trial, the rate of stroke in this trial was higher in the SAVR group than in the TAVI group. The rate of stroke in SAVR group (9.8% at 2 years) was similar to that of the SAVR group of the transapical subcohort of the PARTNER trial[12] (9.9% at 2 years), but patients in the PARTNER trial were at higher risk and had more severe comorbidities that required assignment to the transapical subcohort. The authors stated that the reason for the high rate of stroke in the surgical arm of

the US CoreValve trial was not clear and may have been due to new-onset or worsening atrial fibrillation in SAVR patients (SAVR 32.7%, transfemoral TAVI 15.9% at 1 year).[21] Of note, new-onset atrial fibrillation occurred less frequently in the SAVR group in the PARTNER trial than in the US CoreValve trial (SAVR 17.1%, TAVI 12.1% at 1 year).[20]

In the PARTNER trial cohort B,[13] periprocedural strokes were predominantly embolic ischemic events, but strokes after that period were primarily hemorrhagic, an observation that did not support the continued device-related risk of stroke beyond the first month. Rather, a complex interaction of many factors, including presence of atherosclerotic disease, atrial fibrillation, traumatic head injuries, and concomitant anticoagulation and antiplatelet therapy may explain the higher occurrence of stroke beyond 1 month.

Figures 16 and 17 show the rate of major stroke in TAVI trials.

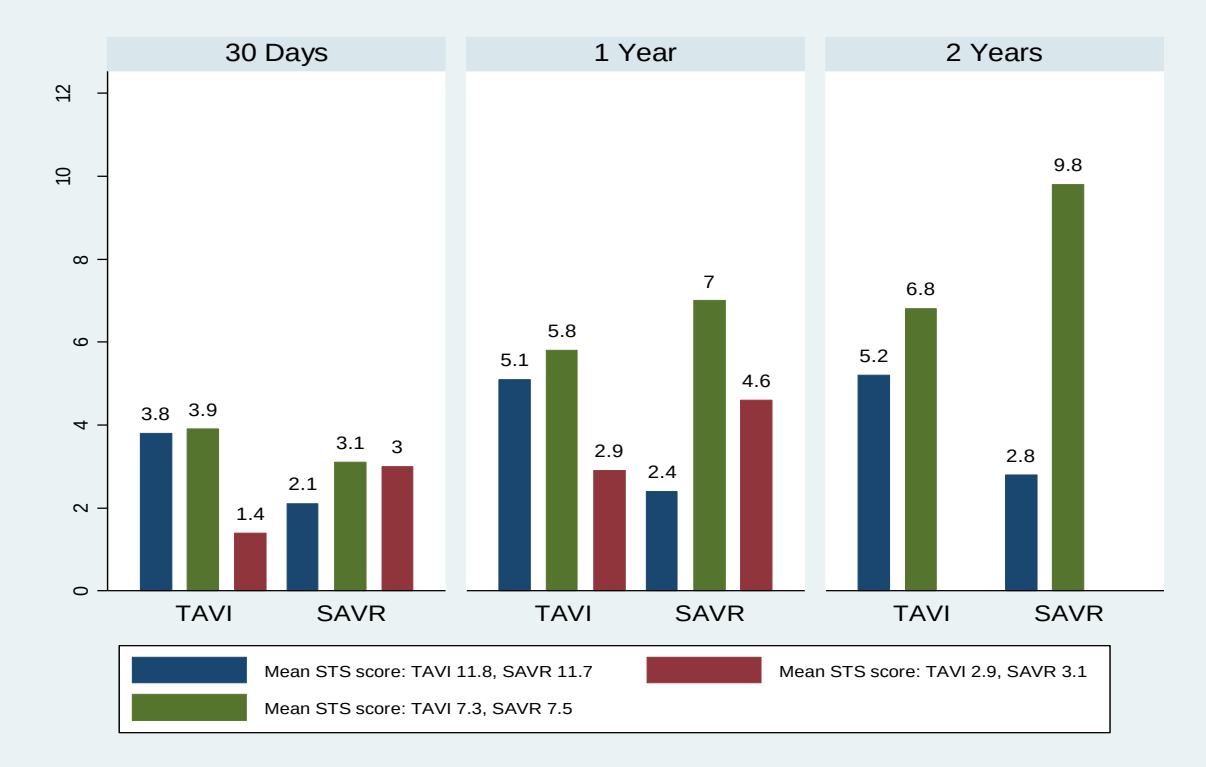

Figure 16: Major Stroke by Category of Surgical Risk, TAVI vs. SAVR

Abbreviations: SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
Sources: Data from Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] and Reardon et al.[34]

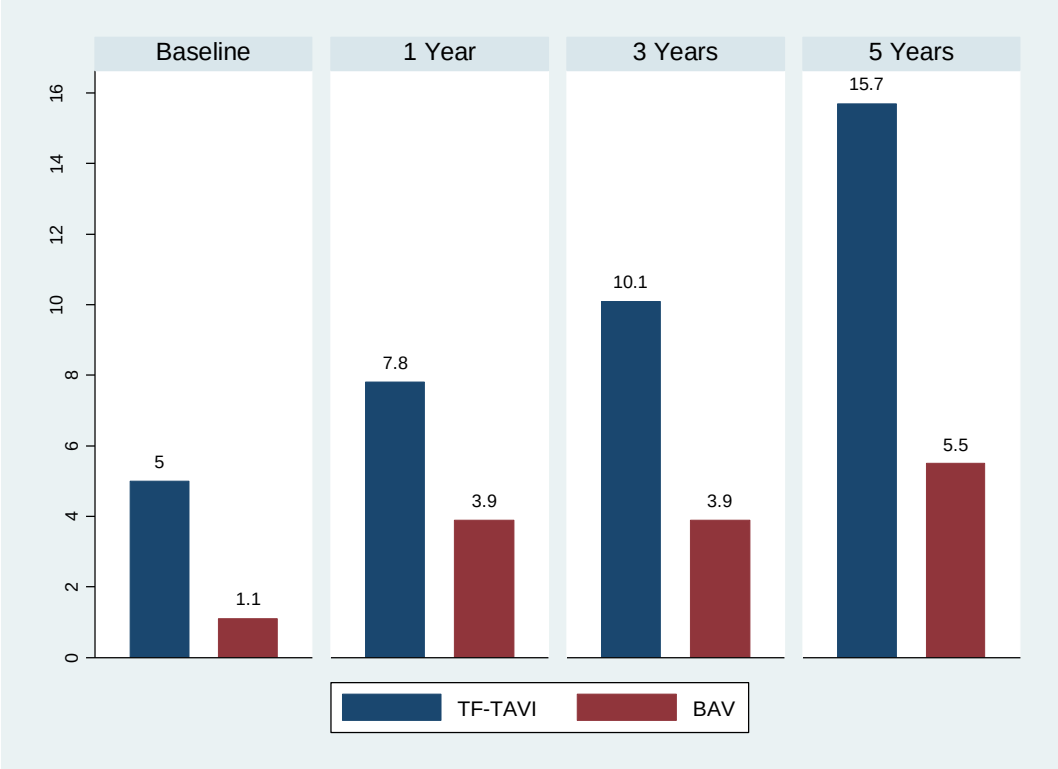

Figure 17: Major Stroke for Transfemoral TAVI vs. BAV

Abbreviations: BAV, balloon aortic valvuloplasty; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
Sources: Data from Leon et al,[19] Makkar et al,[13] and Kapadia et al.[25]

Major Vascular Complications

The rate of major vascular complications was significantly higher in the TAVI group than in the SAVR group in all trials and at all time points (Figures 18 and 19). Comparison among TAVI groups in different trials showed that the rate was lower in the US CoreValve trial[21] than in the PARTNER trials.[19,20] This difference could be explained by the use of an earlier-generation, large-calibre delivery system in trials of high-risk patients (PARTNER cohorts A[20] and B[19]) and the use of smaller-calibre delivery systems in the other trials.[21,22]

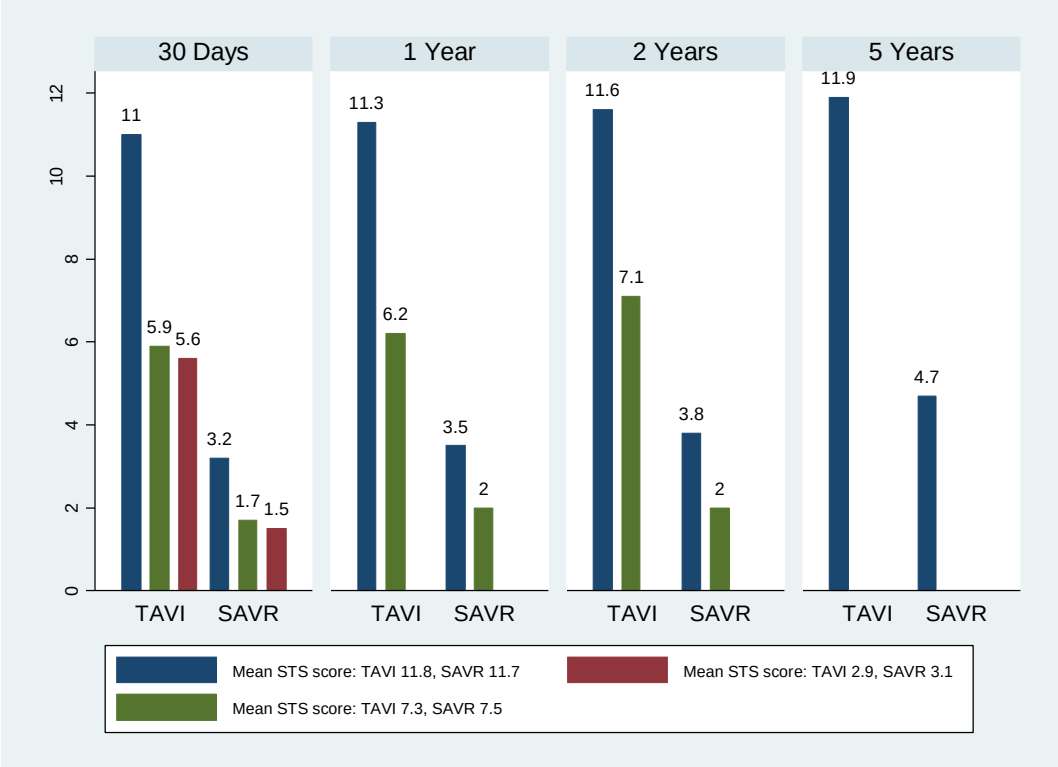

Figure 18: Major Vascular Complications by Category of Surgical Risk, TAVI vs. SAVR

Abbreviations: SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
Sources: Data from Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] Mack et al,[32] and Reardon et al.[34]

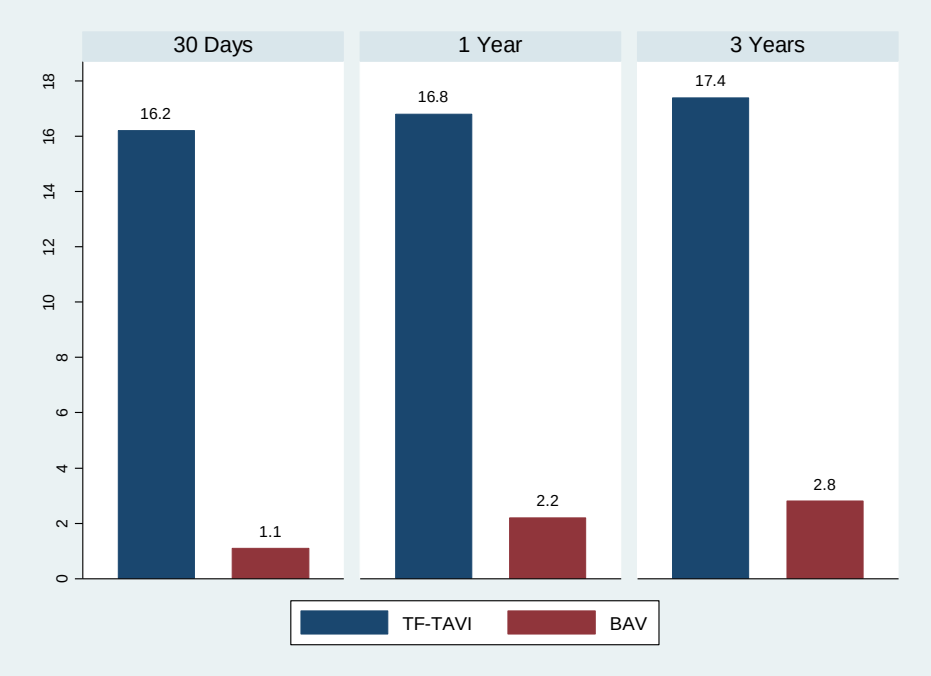

Figure 19: Major Vascular Complications: Transfemoral TAVI vs. BAV

Abbreviations: BAV, balloon aortic valvuloplasty; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
Sources: Leon et al,[19] Makkar et al,[13] and Kapadia et al.[25]

Major Bleeding

Rates of major bleeding were significantly higher in SAVR groups than in TAVI groups in all trials (Figures 20 and 21). However, major bleeding in the SAVR arm of the US CoreValve trial was higher than in the SAVR arm of the other trials.[21] This may have been because of different definitions for major bleeding among the trials. For example, in the US CoreValve trial,[21] the major bleeding definition included bleeding that required a transfusion of 2 or 3 units of whole blood or red cells, while in the PARTNER trial,[20] the definition included transfusion of > 3 units of blood given within 24 hours.

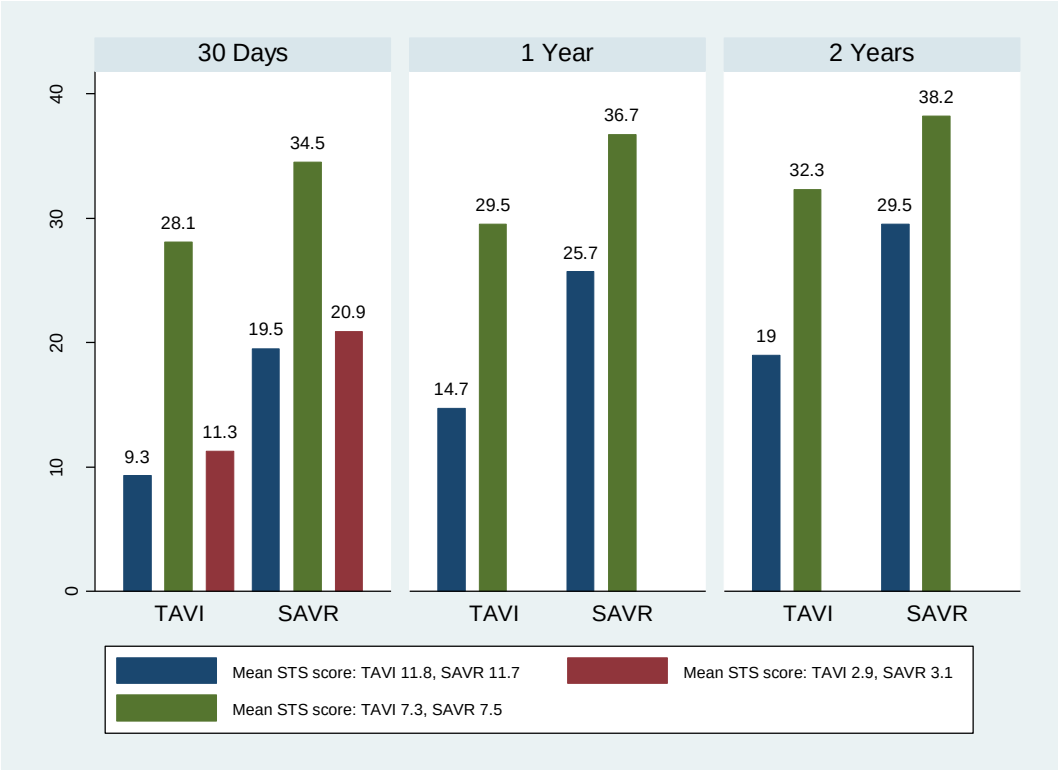

Figure 20: Major Bleeding by Category of Surgical Risk, TAVI vs. SAVR

Abbreviations: SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
Sources: Data from Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] Mack et al,[32] and Reardon et al.[34]

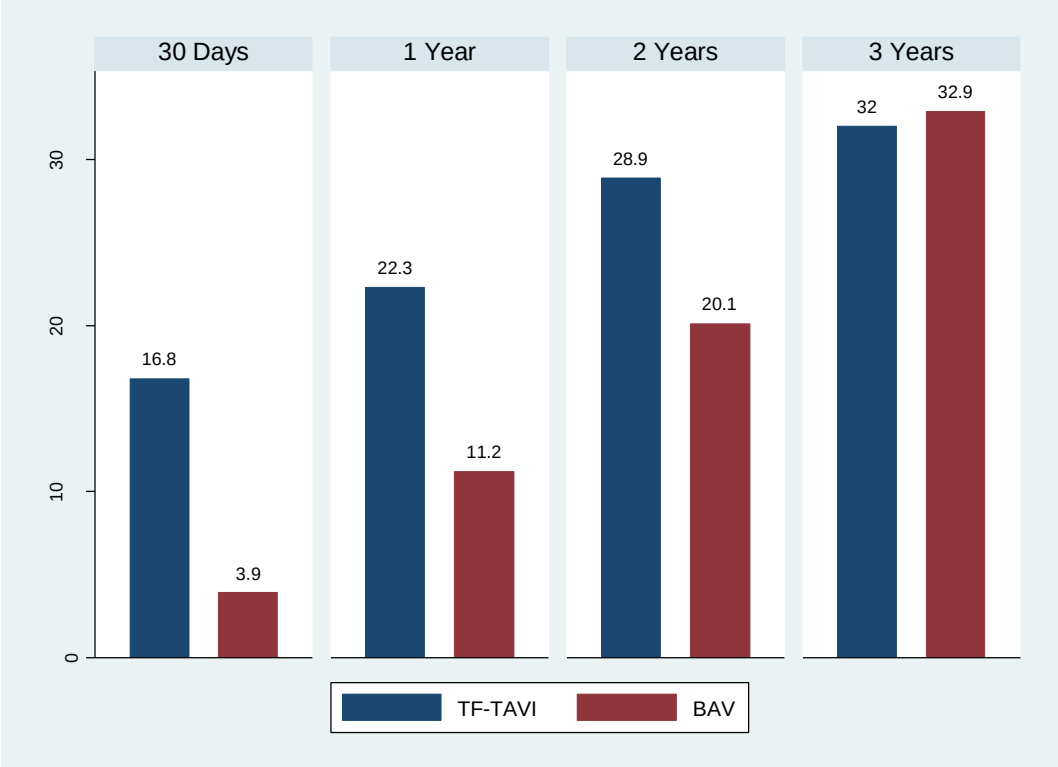

Figure 21: Major Bleeding, Transfemoral TAVI vs. BAV

Abbreviations: BAV, balloon aortic valvuloplasty; TAVI, transcatheter aortic valve implantation; TF, transfemoral.
Sources: Data from Leon et al,[19] Makkar et al,[13] and Kapadia et al.[25]

Pacemaker Implantation

One of the major differences between TAVI and SAVR was the need for pacemaker implantation. The occurrence of conduction abnormalities, which are caused by injury to the conduction system during the procedure, requires implantation of a pacemaker. Patients in the TAVI group of the trials that used CoreValve device had a significantly higher rate of pacemaker implantation after TAVI than after SAVR.[21] The rate of pacemaker implantation was not different between TAVI and SAVR in the trials that used SAPIEN valve (Figure 22).[19,20]

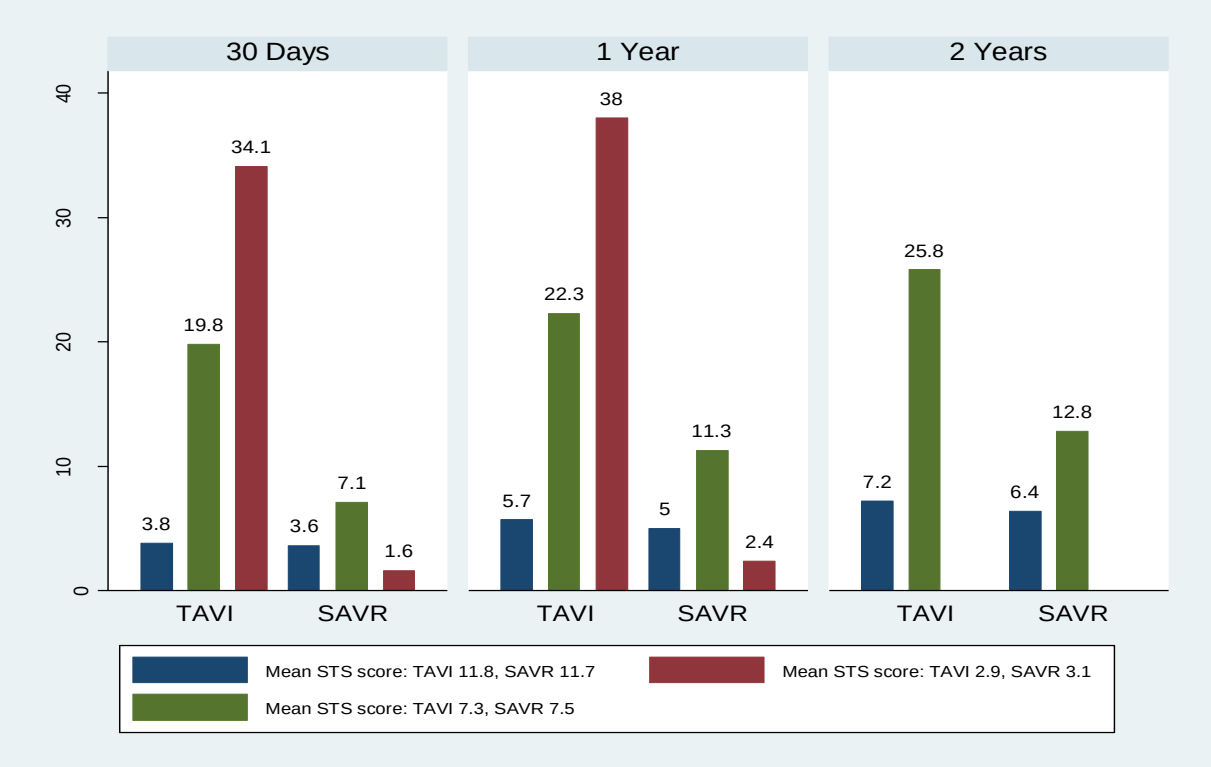

Figure 22: Permanent or New Pacemaker Implantation by Category of Surgical Risk, TAVI vs. SAVR

Abbreviations: SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.
Sources: Data from Smith et al,[20] Adams et al,[21] Thyregod et al,[22] Kodali et al,[12] Mack et al,[32] and Reardon et al.[34]

Discussion

The PARTNER trials and the US CoreValve trial were powered to detect a difference in all-cause mortality between the two treatment groups at 1 year.[19-21] The NOTION trial of low-risk patients[22] was powered to detect a difference in a composite outcome of death, stroke, or myocardial infarction at 1 year. The STACCATO trial of low risk patients was powered for a composite outcome of 30-day all-cause mortality, major stroke, and renal failure requiring dialysis. Most studies showed no difference in mortality between TAVI and SAVR (moderate quality of evidence). Only one[21] showed a statistically significant difference in all-cause mortality (but not cardiovascular mortality) in favour of TAVI, but the risk of stroke in the SAVR arm of this trial was higher than in the other trials, which may partially explain the difference in mortality between the two groups in this trial. The trial of high-risk patients who were not suitable candidates for surgery[19] compared transfemoral TAVI with BAV and showed significantly better survival with TAVI than with BAV (moderate quality of evidence).

In both the PARTNER[20] and US CoreValve[21] trials, the predicted risk of death within 30 days for SAVR (11.7% and 7.5%, respectively) was overestimated: the observed mortality was 6.5% and 4.5%, respectively.

PARTNER trial cohort A[20] showed that transapical TAVI was associated with higher mortality and rates of stroke than transfemoral TAVI. However, the patients in this study had higher rates of comorbid conditions, making it difficult to interpret the results in isolation from the patients'

health profiles. On the other hand, the trial that was designed to compare transapical TAVI with SAVR in a low-risk population was terminated prematurely due to a high frequency of adverse events in the transapical arm.[23] Findings from both trials may help clinicians and decision-makers better assess the risks associated with transapical TAVI.

Both TAVI and SAVR led to improvements in patients' quality of life (low quality of evidence). Quality of life improvements in patients who underwent TAVI depended on whether a transfemoral TAVI or transapical TAVI approach was used. Patients who underwent transfemoral TAVI recovered more quickly than patients who had SAVR. In contrast, patients who underwent transapical TAVI had a slower recovery than patients who had SAVR.

Adverse events including aortic regurgitation, stroke, vascular complications, and pacemaker implantation were more common in patients who had TAVI than patients who had SAVR. In the PARTNER trials, the rate of major stroke was higher in the TAVI group than in the SAVR group at 30 days, 1 year, and 2 years, by a factor of 2.[12,20] The combined rate of stroke and transient ischemic attack was also significantly higher for TAVI than for SAVR. In contrast, in the US CoreValve trial, the rate of major stroke at 1 year and 2 years was higher for the SAVR group.[21,34] At 2 years, patients in SAVR group had a rate of stroke similar to that of the SAVR group in the transapical subcohort of the PARTNER trial.[12,21,34] Since being in a transapical group was one of the strongest determinants of a neurologic event in both TAVI and SAVR groups,[29] the reason for the higher-than-usual rate of stroke in the SAVR arm of the US CoreValve trial [21,34] remains an open question.

High rates of paravalvular aortic regurgitation after TAVI, as seen in all trials, raises a major concern, because this outcome has been associated with increased risk of late cardiac mortality. In the PARTNER trial of high-risk patients suitable for cardiac surgery, the hazard ratio was 2.11 (95% CI, 1.43–3.10; $P < .001$) and the effect was proportional to the severity of the aortic regurgitation.[12] The authors also observed a trend toward higher cardiac mortality among patients with moderate to severe aortic regurgitation in high-risk patients who were not suitable candidates for surgery, a finding that persisted at 2 years.

Major vascular complications were significantly higher in the TAVI group than in the SAVR group in all trials, but the risk of major bleeding was significantly higher in the SAVR group than the TAVI group in all trials. The need for pacemaker implantation was significantly higher in the TAVI group than in the SAVR group of the US CoreValve trials.[21,34]

Strengths and Limitations

The PARTNER trials, cohorts A[20] and B,[19] used a first-generation transcatheter device (both valve and delivery system). The device used in these trials has been replaced by newer-generation devices and is no longer used in current clinical practice. Therefore, the clinical outcomes and performance of TAVI in these trials might not reflect the performance of subsequent generations of the SAPIEN valve and delivery systems. In addition, the PARTNER trial started in 2007 and represents early clinical practice; undoubtedly, the learning curve could have adversely affected outcomes. The CoreValve device has also undergone recent changes. The new generation of these devices and their delivery systems are being tested in clinical trials.

Conclusions

- Moderate quality evidence showed that TAVI and SAVR had similar rates of cardiovascular mortality in patients who were eligible for surgery
- In patients who were not suitable candidates for surgery, TAVI improved survival compared with balloon aortic valvuloplasty (GRADE: moderate)
- Moderate quality evidence showed that, compared with SAVR, TAVI was associated with higher rates of stroke, vascular complications, and paravalvular aortic regurgitation, which is still a cause for concern in TAVI. Some TAVI procedures were associated with higher rates of pacemaker insertion (GRADE: moderate). SAVR was associated with a higher risk of bleeding than TAVI (GRADE: moderate)
- Low quality evidence showed that TAVI and SAVR both led to substantial improvements in quality of life during the first year. However, because of a large amount of missing data and the lack of availability of published data beyond 1 year, it is difficult to evaluate the impact of critical outcomes on patients' longer-term health status

ECONOMIC EVIDENCE REVIEW

Objectives

The objective of this study was to review the literature on the cost-effectiveness of transcatheter aortic valve implantation (TAVI) compared with surgical aortic valve implantation (SAVR) or medical management in patients with severe aortic valve stenosis.

Methods

Sources

We performed an economic literature search on October 2, 2015, using Ovid MEDLINE (1946 to present), Ovid MEDLINE In-Process (1946 to present), Ovid Embase (1980 to 2015 week 25), Cochrane Central Register of Controlled Trials (to May 2015), Cochrane Database of Systematic Reviews, (2005 to May 2015), Database of Abstracts of Reviews of Effects (DARE) (to second quarter 2015), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database (to second quarter 2015), and National Health Service (NHS) Economic Evaluation Database (to second quarter 2015) for studies published from January 1, 2011, to October 2, 2015. We also reviewed reference lists of included economic literature for any additional relevant studies not identified through the systematic search.

Literature Screening

We based our search terms on those used in the clinical evidence review of this report and applied economic filters to the search results. Study eligibility criteria for the literature search are listed below. A single reviewer reviewed titles and abstracts and, for those studies meeting the inclusion/exclusion criteria, we obtained full-text articles.

Inclusion Criteria

- English-language full-text publications
- Published between January 1, 2011, and October 2, 2015
- Studies in patients with severe aortic valve stenosis
- Studies reporting on TAVI as an intervention
- Economic evaluations reporting incremental cost-effectiveness ratios (ICERs) (e.g., cost per quality-adjusted life-year (QALY)/life-year gained or cost per event avoided)

Exclusion Criteria

- Narrative reviews, letters/editorials, abstracts, posters, unpublished studies
- Studies in pediatric populations
- Foreign-language publications

Outcomes of Interest

- Full economic evaluations: cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses

Data Extraction

We extracted relevant data on the following:

- Study characteristics (i.e., authors, year of publication)
- Population and comparators
- Interventions
- Outcomes (i.e., health outcomes, costs, and cost-effectiveness)

Limitations

Only one reviewer screened the literature and abstracted the data.

Results

Literature Search

The database search yielded 259 citations published between January 1, 2011, and October 2, 2015 (with duplicates removed). We excluded a total of 246 articles based on information in the title and abstract. We then obtained the full texts of 13 potentially relevant articles for further assessment. Figure 23 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

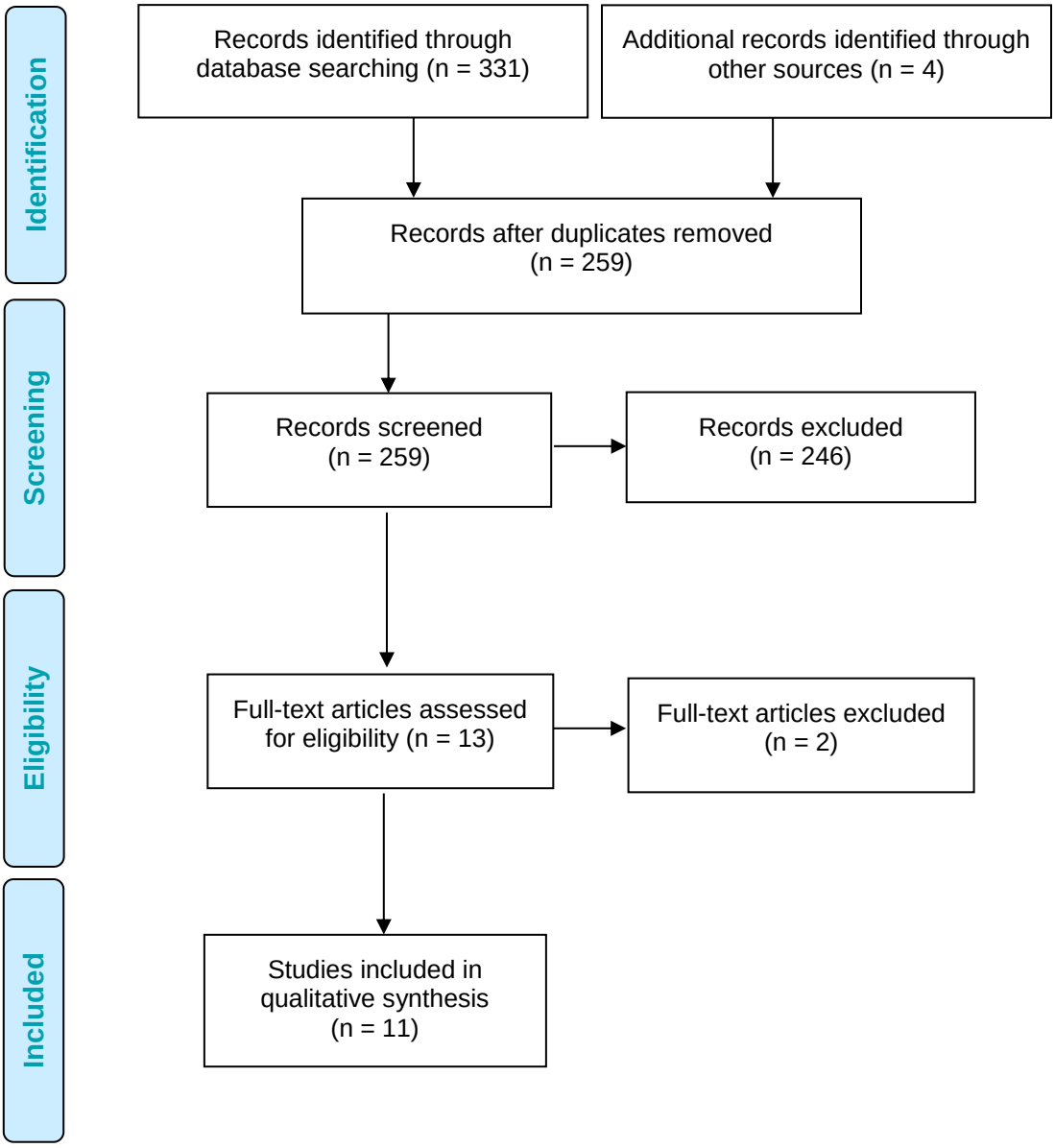

Figure 23: PRISMA Flow Diagram for the Economic Review

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[18]

Critical Review

Table 13 presents the results of the economic literature review.

Table 13: Results of Economic Literature Review—Summary

Name, Year, Location	Study Design and Perspective	Population	Intervention/ Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Brecker et al, 2014,[38] United Kingdom	• Cost-effectiveness analysis (utility measured as QALYs) • Adapted published decision-analytic Markov model • 5-year time horizon • United Kingdom NHS perspective	• N = 1,015 (all patients from ADVANCE), 369 (high-risk from ADVANCE) and 179 (all patients from PARTNER cohort B) • Mean age 81 years and older • Patients with severe aortic stenosis	TAVI/MM	Expected QALYs Probabilistic sensitivity analysis • ADVANCE high-risk, 0.78; all PARTNER-B, 2.02 • All ADVANCE, 0.78; all PARTNER-B, 2.29	2014 UK pounds, expected costs Probabilistic sensitivity analysis • ADVANCE high-risk, £13,120; all PARTNER-B, £35,129 • All ADVANCE, £13,154; all PARTNER-B, £34,192 Discount rate: 3.5%	Probabilistic sensitivity analysis • ADVANCE high-risk vs. all PARTNER-B: £17,718/QALY • ADVANCE high-risk vs. all PARTNER-B: £13,943/QALY
Doble et al, 2013,[39] Canada	• Cost-effectiveness analysis • Combined decision tree and Markov model • 20-year time horizon • Canadian healthcare perspective	• TAVI vs. MM in inoperable patients with severe, symptomatic aortic stenosis • TAVI vs. SAVR in operable patients with severe, symptomatic aortic stenosis	TAVI (Edwards SAPIEN valve)/SAVR and MM	Primary analysis • Expected life-years: Δ life-year (TAVI vs. MM), 0.85 • Expected QALYs: Δ life-year (TAVI vs. MM), 0.60 Secondary analysis • Expected life-years: Δ life-year (TAVI vs. MM), 0.0128 Expected QALYs: Δ life-year (TAVI vs. MM): (0.102)	Primary analysis • Expected costs: TAVI, $88,991; MM, $57,963 Secondary analysis • Expected costs: TAVI, $85,755; SAVR, $74,602 Discount rate: 5%	Primary analysis • ICER (TAVI vs. MM): $36,458/life-year and $51,324/QALY Secondary analysis • ICER (TAVI vs. SAVR): $870,143/life-year and TAVI was dominated by SAVR regarding QALY measure
Fairbairn et al, 2013,[40] United Kingdom	• Cost-utility analysis • Markov model • 10-year time horizon • United Kingdom NHS perspective	• High-risk aortic stenosis population • Data taken from PARTNER A study	TAVI/SAVR	• Expected QALYs: TAVI: 2.81 SAVR: 2.75	2013 UK pounds TAVI: £52,593 SAVR: £53,493 Discount rate: 3.5%	TAVI dominated SAVR Probabilistic sensitivity analysis: at £20,000/QALY, 64.6% TAVI vs. 35.4% SAVR being cost-effective
Gada et al, 2012,[41] United States	• Cost-effectiveness analysis • Markov model • Lifetime horizon • United States healthcare perspective	• High-risk aortic stenosis population • Mean age of 80 years old	TAVI (Edwards SAPIEN valve)/AVR and MM	Expected QALYs: TAVI, 1.78; AVR, 1.72	2011 US dollars Expected costs: TAVI, $59,503; AVR, $56,339 Discount rate: 5%	Reference case (probabilistic sensitivity analysis): ICER (TAVI vs. AVR) $52,773/QALY

Name, Year, Location	Study Design and Perspective	Population	Intervention/ Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Hancock-Howard et al, 2013,[42] Canada	• Cost-effectiveness analysis • Deterministic decision-analytic model • 3-year time horizon • Canadian healthcare perspective	• Inoperable patients with severe aortic stenosis	TAVR/MM	Base-case analysis, expected QALYs: TAVR, 1.325; MM, 0.837	Base-case analysis, expected costs: TAVR, $42,670; MM, 58,357 Discount rate: 5%	Base-case analysis: ICER (TAVR vs. MM): $32,170 per QALY 24-month time horizon: ICER (TAVR vs. MM): $52,848 12-month time horizon ICER (TAVR vs. MM): $157,429
Murphy et al, 2013,[43] United Kingdom	• Cost-effectiveness analysis • Combined short-term decision tree and long-term Markov model • 30 years to lifetime horizon • United Kingdom NHS perspective	• Inoperable patients with severe aortic stenosis	TAVI/MM	Probabilistic sensitivity analysis • Life-years: TAVI, 2.54; MM, 2.24 • QALYs: TAVI, 1.63; MM, 1.19	UK pounds Probabilistic sensitivity analysis, expected costs: TAVI, £28,061; MM, £12,176 Discount rate: 3.5%	ICER (TAVI vs. MM): £35,956 per QALY
Neyt et al, 2012,[44] Belgium	• Cost-utility analysis • Markov model • Lifetime horizon	• Patients with severe aortic stenosis	TAVI/SAVR and MM	• TAVI vs. SAVR: Δ QALYs, 0.03 • TAVI vs. MM: Δ QALYs, 0.74; Δ life-years, 0.88	Euros TAVI vs. SAVR: Δ costs, €20,397 TAVI vs. MM: Δ costs, €33,200 Discount rate: 3.5% for costs, 1.5% for effects	TAVI vs. SAVR: ICER, €750,000 per QALY gained TAVI vs. MM: ICER, €44,900 per QALY gained; ICER, €42,600 per LYG

Name, Year, Location	Study Design and Perspective	Population	Intervention/ Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Reynolds et al, 2012,[45] United States	• Cost-effectiveness analysis • Decision tree model • 1-year time horizon • United States healthcare perspective	• Patients with severe aortic stenosis and high surgical risk	TAVR/SAVR	LYGs • All patients: TAVR, 0.858; SAVR, 0.817 • Transfemoral cohort: TAVR, 0.878; SAVR, 0.813 • Transapical cohort: TAVR, 0.811; SAVR, 0.826 QALYs • All patients: TAVR, 0.633; SAVR, 0.606 • Transfemoral cohort: TAVR, 0.659; SAVR, 0.591 • Transapical cohort: TAVR, 0.570; SAVR, 0.641	2010 US dollars • All patients (TAVR-SAVR): Δ costs, $2,070 • TF cohort: Δ costs, –$1,250 • TA cohort: Δ costs, $9,906	ICER (TAVR vs. SAVR) • All patients: $76,877 per QALY gained • TF cohort: TAVR dominant • TA cohort: TAVR dominated
Reynolds et al, 2012,[46] United States	• Cost-effectiveness analysis • Decision-analytic Markov model • Lifetime horizon • United States healthcare perspective	• Inoperable patients with severe aortic stenosis	TAVR (Edwards SAPIEN) and TAVR (CoreValve)/MM	LYGs: TAVR, 2.78; MM, 1.20 QALYs: TAVR, 2.03; MM, 0.73	TAVR: $149.740 MM: $69,903 Discount rate: 3%	$50,212 per LYG $61,889 per QALY gained
Ribera et al, 2015, [47] Spain	• Cost-utility analysis • Decision tree model • 1-year time horizon • Spanish healthcare perspective	• Patients with severe aortic stenosis	TAVR/SAVR	Edwards SAPIEN: Δ QALY, 0.036 CoreValve: ΔQALY, –0.011	2012 Euros Edwards SAPIEN: Δ costs, €8,800 CoreValve: dominated; Δ costs, €9,729	Edwards SAPIEN: ICER, €148,525/QALY CoreValve: dominated
Watt et al, 2012[48] United States	• Cost-effectiveness analysis • Decision-analytic Markov model • 10-year time horizon • United Kingdom NHS perspective	• Nonsurgical patients with severe, symptomatic aortic stenosis	TAVR/MM	QALYs: TAVR, 2.36; MM, 0.80	2010 British pounds TAVR: £30,200 MM: £5,000	ICER: £16,200 per QALY gained

Abbreviations: AVR, aortic valve replacement; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; MM, medical management; QALY, quality-adjusted life-year; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; TF, transfemoral; NHS, National Health Service.

Brecker et al[38] measured the cost-effectiveness of TAVI implantation by comparing the costs and benefits in patients who received TAVI as part of the ADVANCE study,[49] with those receiving medical management in cohort B of the PARTNER trial.[19] The authors adapted a published decision-analytic model to include information on TAVI from the ADVANCE study. Patient-level data informed the choice and form of mathematical functions used to model all-cause mortality, health-related quality of life, and hospitalizations. Outcome measures were ICERs and QALYs. Over a 5-year time horizon, the ICER comparing all ADVANCE to all PARTNER-B patients was £13, 943 per QALY gained. For a subset of high-risk ADVANCE patients, the ICER was £17,718 per QALY gained. These ICER values were below £20,000 per QALY gained. TAVI was highly likely to be a cost-effective treatment for patients with severe aortic stenosis.

Doble et al[39] conducted a cost-effectiveness analysis comparing TAVI with medical management and SAVR. The authors developed a combined decision tree and Markov model to compare costs, life-years, and QALYs over a 20-year time horizon from the Canadian healthcare payer perspective. When comparing TAVI with medical management, the ICER was $36,458 per life-year and $51,324 per QALY, respectively. When comparing TAVI with SAVR, the ICER was $870,143 per life-year gained and in terms of QALYs, TAVI was dominated by SAVR.

Fairbairn et al[40] evaluated the cost-effectiveness of TAVI compared with SAVR in a high-risk aortic stenosis population from a United Kingdom National Health Service perspective. The authors developed a Markov model and followed it for a 10-year time horizon. Utility data were taken from a United Kingdom high-risk aortic stenosis population. The clinical effectiveness of TAVI and SAVR was taken from the PARTNER trial cohort A.[20] The model estimated that over the 10-year time horizon, TAVI would generate more QALYs than SAVR at a lower cost, making TAVI a dominant strategy.

Gada et al[50] conducted a cost-effectiveness analysis comparing TAVI with SAVR and medical management. They constructed a Markov model in the treatment of high-risk aortic stenosis patients and derived outcomes and costs from 10,000 simulations. Both TAVI and SAVR were cost-effective compared to medical management, and at a threshold of $100,000 per QALY, TAVI was cost-effective compared to SAVR.

Hancock-Howard et al[42] carried out a cost-effectiveness analysis comparing transcatheter aortic valve replacement with medical management in surgically inoperable patients with severe aortic stenosis from the Canadian public healthcare system perspective. They constructed a deterministic decision-analytic model to follow aortic stenosis patients over a 3-year time horizon. Data on survival, utilities, and some resource utilization were taken from the PARTNER A randomized clinical trial.[20] Costs data were retrieved from the Ontario Case Costing Initiative. The authors explored the effect of uncertainty in model parameters using both deterministic and probabilistic sensitivity analyses. Comparing transcatheter aortic valve replacement with medical management, the ICER was $32,170 per QALY gained. When the time horizon was shortened to 24 and 12 months, the ICERs increased to $52,848 and $157,429, respectively, for transcatheter aortic valve replacement compared with medical management, but all other sensitivity analyses resulted in ICER values of less than $50,000 per QALY gained.

Murphy et al[43] conducted a cost-effectiveness analysis comparing TAVI with medical management in the treatment of patients with severe aortic stenosis, who were inoperable from the United Kingdom National Health Service perspective. They developed a combined short-term decision tree and a long-term Markov model to follow patients from 30 days to death. The

authors reported a probabilistic sensitivity analysis using 10,000 simulations as the base-case results. Main health outcomes were QALYs and life-years gained, as well as treatment costs. Comparing TAVI with medical management, the results of the cost-effectiveness analysis for inoperable patients suggested that TAVI was both more costly and more effective than medical management. This translated to an ICER of £35,956 per QALY gained, marginally above the level usually considered cost-effective in the United Kingdom (£20,000 to £30,000 per QALY).

Neyt et al[44] conducted a cost-utility analysis comparing TAVI with SAVR for high-risk operable severe aortic stenosis patients and with medical management for high-risk inoperable severe aortic stenosis patients. They developed a Markov model to compare different treatment strategies (TAVI versus SAVR and TAVI versus medical management) in the treatment of these two groups of patients. The analysis was done from the healthcare payer's perspective and followed for a lifetime horizon. The data on survival, number of events, and quality of life were taken from the PARTNER trial.[19,20] In the base-case analysis, comparing TAVI with SAVR, there was a minimal incremental increase in QALYs (0.03) with an excessive incremental increase in treatment cost (€20,397). This translated to an ICER of €750,000 per QALY gained. Comparing TAVI with medical management, there were incremental increases of 0.88 LYG and 0.74 QALY at a corresponding incremental cost of €33,200. This translated to ICERs of €42,600 per LYG and €44,900 per QALY gained, respectively.

Reynolds et al[45] evaluated the cost-effectiveness of transcatheter aortic valve replacement compared with SAVR for patients with severe aortic stenosis and at high surgical risk. The authors used data on costs, quality of life, and survival from the PARTNER A trial.[20] In the base-case analysis, treatment cost in the transcatheter aortic valve replacement arm was slightly higher than in the SAVR arm, with a small increase in QALYs gained. This translated to an ICER of $76,877 per QALY gained. However, the cost-effectiveness results differed substantially according to access site. Among patients suitable for a transfemoral approach, TAVR resulted in a cost savings of $1,250 per patient and a modest gain in QALYs compared with SAVR. Among patients who were unsuitable for transfemoral access, the transapical approach resulted in higher 12-month costs and lower QALYs than SAVR and was dominated by SAVR.

Reynolds et al[46] conducted a cost-effectiveness analysis comparing transcatheter aortic valve replacement with medical management among inoperable patients with severe aortic stenosis. They used 12-month data on survival, quality of life, and costs to forecast lifetime costs and health outcomes. In the base-case analysis, it was projected that over a patient's lifetime, transcatheter aortic valve replacement would increase discounted life expectancy by 1.58 years (1.3 QALYs) at an incremental cost of $79,837. This translated to ICERs of $50,212 per LYG and $61,889 per QALY gained. The results were also stable through one-way and probabilistic sensitivity analyses.

Ribera et al[47] also carried out a cost-utility analysis comparing transcatheter aortic valve replacement and SAVR among patients with severe aortic stenosis and at intermediate surgical risk. The authors compared two types of devices (Edwards SAPIEN and Medtronic CoreValve) with SAVR. In the base-case analysis, comparing transcatheter aortic valve replacement with SAVR using Edwards SAPIEN resulted in an ICER of €148,525 per QALY, and transcatheter aortic valve replacement was dominated by SAVR if using Medtronic CoreValve device. However, sensitivity analyses showed that in patients with high preoperative serum creatinine, ICERs were €18,302 per QALY and €179,618 per QALY for Edwards SAPIEN and Medtronic CoreValve, respectively. When the cost of the devices was reduced by 30%, the ICER for Edwards SAPIEN was €32,955 per QALY.

Watt et al[48] carried out a cost-effectiveness analysis comparing transcatheter aortic valve replacement with medical management among inoperable patients with severe aortic stenosis. The authors developed a decision Markov model to follow patients for 10-year time horizon. Health-related quality of life and mortality were taken from the PARTNER clinical trial (cohort B).[19] Costs and benefits were discounted at 3.5% per year. The study was done from the United Kingdom National Health Service perspective. The base-case ICER was approximately £16,200 per QALY gained. The results were robust to changes in key clinical parameters. TAVR was highly likely to be cost-effective for patients with severe aortic stenosis and who were ineligible for SAVR.

Discussion and Conclusions

TAVI was cost-effective compared with medical management in inoperable patients in most of the included studies except for that of Murphy et al,[43] where the ICER was slightly higher than the commonly accepted threshold in the United Kingdom (£20,000 to £30,000 per QALY). This study used clinical data based on the early results of the PARTNER trial (cohort B).[19]

Comparing TAVI with SAVR in high-risk patients, cost-effectiveness varied across studies. This was likely attributable to the assumptions made and the uncertainty of the model parameters used.

Two cost-effectiveness studies were conducted using a Canadian perspective.[39,42] Both concluded that TAVI was cost-effective when compared with medical management. The study by Doble et al[39] concluded that TAVI was dominated by SAVR.

Since 2011, new clinical data on longer-term outcomes for both TAVI and SAVR have become available for high-risk patients. Therefore, it was deemed important to conduct an economic evaluation to assess the cost-effectiveness of TAVI compared with SAVR using the new available clinical evidence specifically for the Ontario context.

PRIMARY ECONOMIC EVALUATION

Objectives

This objective of this study was to assess the cost-effectiveness of TAVI compared with SAVR in patients with severe aortic stenosis and high surgical risk from the perspective of the Ontario Ministry of Health and Long-Term Care.

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.[51]

Type of Analysis

We conducted a cost-utility analysis to estimate the annual costs and health outcomes (e.g., QALYs, life-years) of TAVI.

Target Population

The study population was men and/or women presenting with severe aortic stenosis who were determined to be at high surgical risk based on a heart team assessment.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions

We conducted evaluations to compare TAVI with SAVR among patients who had severe aortic stenosis and were at high surgical risk.

Discounting and Time Horizon

We applied an annual discount rate of 5% to both costs and QALYs.[52] We used a 5-year time horizon for the base-case analysis.

Model Structure/Structure of the Analysis

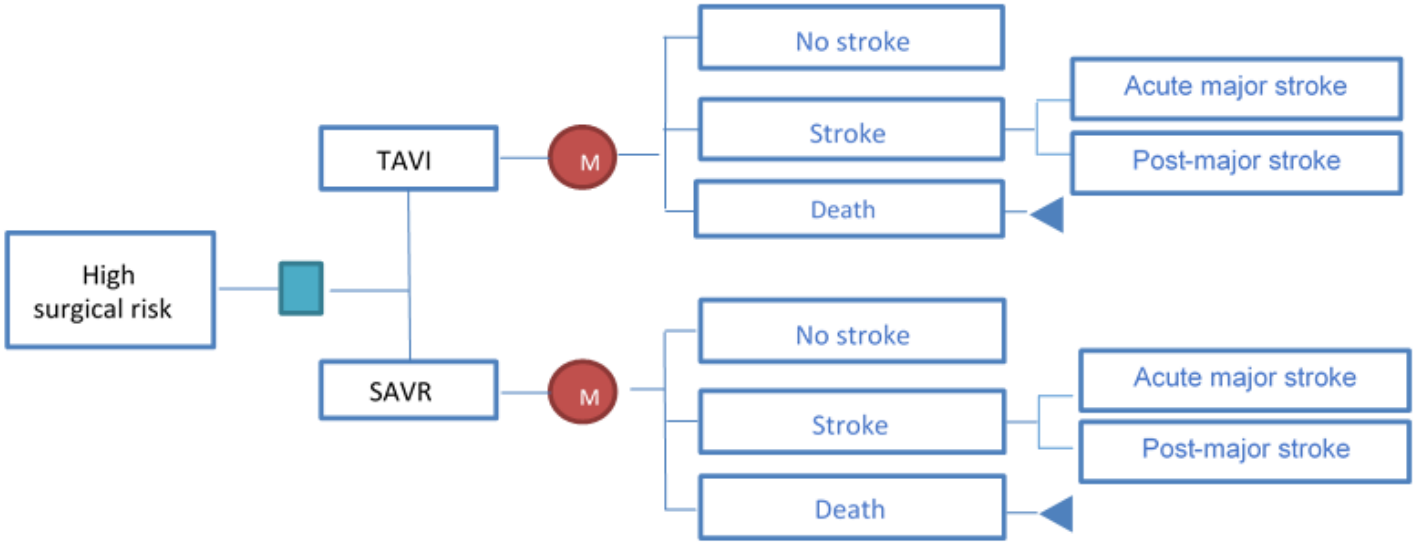

Figure 24: Markov Model for TAVI vs. SAVR in High-Risk Patients With Severe Aortic Stenosis

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
Decision node: square; chance node: circle with M; termination node: triangle.

The Markov model included three health states (Figure 24). Patients with severe aortic stenosis at high surgical risk, who received either TAVI or SAVR would enter one of the following:

- No acute major stroke event (no stroke state)
- Acute major stroke major event (major stroke state)
- Death (patients transfer to this state because of procedure-related death or for other reasons)

In the model, patients with severe aortic stenosis would receive either TAVI or SAVR. During or after the completion of either procedure, the patient would either live or die. If the patient died, they would remain in this state. Death could be as a result of the procedure or for other reasons. If the patient lived, they could enter into one of two states: 1) no acute major stroke or 2) acute major stroke. From the no acute major stroke state, the patient would die, remain in this health state or move into the acute major stroke state if an episode of major stroke occurred. The major stroke state consisted of two substates: acute major stroke and post–major stroke. A patient would first experience an acute major stroke and then die or stay in the acute major stroke state for 1 month after the event (hospitalization). After discharge from hospital, the patient would enter into the post–major stroke state. Patients would then either die or remain in this state.

We followed the cohort of patients with severe aortic stenosis for 5 years under the assumption that these patients were elderly and that TAVI is indicated for patients with a life expectancy of greater than 2 years (Dr. Wijeysundera, personal communication, March 4, 2016). The cycle of the model was 1 month.

Data Source

We used clinical data from the US CoreValve Pivotal Trial[21,34] for the following reasons:

- In Ontario, the two approved devices are the Medtronic CoreValve and the Edwards SAPIEN XT. Both of these valves are second-generation devices, are of identical efficacy, and represent contemporary therapy
- The original PARTNER trial[19] used first-generation valves in unwell patients with aortic stenosis. This was not representative of current practice in Ontario, where the devices are second-generation devices. The SAPIEN XT and CoreValve have a smaller profile and are associated with fewer adverse events

Transition Probabilities

We obtained transition probabilities from a randomized, controlled, multicentre study conducted in 45 centres in the United States[21] and from a 2-year outcomes follow-up study by Reardon et al.[34]

We used clinical data from Adams et al[21] and Reardon et al[34] (death from any cause, major stroke, and adverse events such as major vascular complications, life-threatening or disabling bleeding, and permanent pacemaker implantation) at 30 days and at 1 year to calculate the monthly transition probability in the first year. We used clinical data at 1 year and at 2 years to calculate the monthly transition probability in the second year using formulae reported elsewhere.[53] Transition probabilities are shown in Table 14.

Table 14: Model Variable Inputs Used in the Base-Case and Probabilistic Sensitivity Analyses

	TAVI		SAVR		
Transition Probability	**Mean**	**Distribution**	**Mean**	**Distribution**	**Reference**
All-Cause Mortality					
At 30 days	0.033	Beta	0.045	Beta	Adams et al, 2014[21]
Monthly mortality in the first year	0.010128	Beta	0.013596374	Beta	Adams et al, 2014[21]
Monthly mortality in the second year	0.007770	Beta	0.009785744	Beta	Adams et al, 2014[21] Reardon et al, 2015[34]
Major Stroke					
At 30 days	0.039	Beta	0.031	Beta	Adams et al, 2014[21]
Monthly probability of major stroke in the first year	0.001697	Beta	0.003152916	Beta	Adams et al, 2014[21]
Monthly probability of major stroke in the second year	0.000885	Beta	0.002508961	Beta	Adams et al, 2014[21] Reardon et al, 2015[34]
Adverse Events					
Monthly probability of major vascular complications in the first year	0.000247709	Beta	0.00025900	Beta	Adams et al, 2014[21]
Monthly probability of major vascular complications in the second year	0.000667337	Beta	0	Beta	Adams et al, 2014[21] Reardon et al, 2015[34]
Monthly probability of life-threatening or disabling bleeding in the first year	0.002967359	Beta	0.00431034	Beta	Adams et al, 2014[21]
Monthly probability of life-threatening or disabling bleeding in the second year	0.001233009	Beta	0.001214199	Beta	Adams et al, 2014[21] Reardon et al, 2015[34]
Monthly probability of pacemaker implantation in the first year	0.003474233	Beta	0.00411273	Beta	Adams et al, 2014[21]
Monthly probability of pacemaker implantation in the second year	0.002938381	Beta	0.001038422	Beta	Adams et al, 2014[21] Reardon et al, 2015[34]

Abbreviations: QALY, quality-adjusted life-year; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

To estimate life expectancy, we applied monthly mortality in the first year and second year, based on values from Adams et al[21] and Reardon et al.[34] Since mortality data were not available beyond 24 months, we used the multiplicative factor of 1.15 derived for SAVR group mortality. This multiplicative factor was calculated using the survival between 6 and 24 months in the SAVR group, which was calibrated to expected age- and sex-adjusted mortality using life tables from the United States.[54] We assumed that in the base-case analysis, beyond 2 years, the

hazard ratio comparing TAVI and SAVR mortality would equal 1. For the sensitivity analysis, we varied this ratio within a range of 0.86 to 1.27 based on the data provided by Reynolds et al.[54]

In the absence of clinical data beyond 2 years, we assumed that for stroke, the monthly transition probability beyond 2 years would remain the same as the monthly transition probability in year 2 in for both the TAVI and SAVR arms. We made this assumption because TAVI has been shown to be better in clinical outcomes at 2-year follow-up.[34] We assumed that there were no adverse events beyond 2 years (major vascular complications or life-threatening or disabling bleeding) except for the probability of pacemaker implantation. The monthly probability of pacemaker implantation beyond 2 years was assumed to be the same as that applied in year 2.

Clinical Outcome and Utility Parameters

We quantified health outcomes as QALYs. In a study by Arnold et al,[33] the authors collected health utility data from 795 patients with severe aortic stenosis and increased surgical risk, who were randomized to TAVI or SAVR in the US CoreValve Pivotal Trial.[21] In this study, health status was assessed at baseline, 1 month, 6 months, and 1 year using the EuroQOL 5-dimension questionnaire (Table 15).[55] The results showed that patients eligible for TAVI would receive health status benefits compared with SAVR for all generic health status measures, and there was no differences between the two groups at later time points.[33] We used these generic health status outcomes as utility values in our analysis, since our model also had a monthly cycle and the utility data were based on quality-of-life outcomes that directly captured the views of patients who underwent either TAVI or SAVR.

Data measuring the quality of life of patients who received either TAVI or SAVR were available for only up to 12 months. Therefore, we assumed that these utility values would be in effect until 24 months, since clinical data showed that TAVI was more effective than SAVR at 2 years.[34] We made a conservative assumption that beyond 24 months, the utility values would be identical for all patients, regardless of whether they received TAVI or SAVR.

Table 15: Utilities Used in the Economic Model

	TAVI		SAVR		
Health State	Utility	Distribution	Utility	Distribution	Reference
Baseline	0.730 (0.708–0.752)	Beta	0.730 (0.710–0.750)	Beta	Arnold et al, 2015[33]
1 month	0.785 (0.754–0.817)	Beta	0.657 (0.614–0.700)	Beta	
6 months	0.783 (0.753–0.812)	Beta	0.770 (0.744–0.795)	Beta	
12 months	0.773 (0.745–0.801)	Beta	0.733 (0.701–0.765)	Beta	

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Cost Parameters

Costs included those for the device (TAVI and SAVR), the procedures, procedure-related adverse events (e.g., major vascular complications, life-threatening or disability bleeding, pacemaker implantation), treatment costs for adverse events, treatment costs for acute major stroke, follow-up costs for major stroke in the months after a stroke occurs, and follow-up costs of adverse events. Table 16 summarizes the main cost parameters for the cost-effectiveness model.

Table 16: Costs Used in the Economic Model

Variable	Base-Case Value, $	Range, $	Distribution	Reference
Episode Costs				
CoreValve (TAVI), procedure cost, and any procedure-related adverse-event costs	47,198	44,617–49,780	Gamma	Li et al, 2015[56]
Bioprosthesis (SAVR) procedure cost, and any procedure-related adverse-event costs	40,132	35,007–45,258	Gamma	
Major Stroke				
Hospitalization costs	31,081	2,458–149,412	Gamma	Mittmann et al, 2012[57]
Monthly follow-up costs in the first year	4,246	10–22,570	Gamma	
Monthly follow-up costs in subsequent years	4,101	15–21,678	Gamma	
Adverse Events				
Monthly cost of treatment for major vascular complications	5,692	4,269–7,115	Gamma	Doble et al, 2013[39]
Monthly cost of treatment of life-threatening or disabling bleeding	5,128	3,419–6,838	Gamma	Singh et al, 2013[58]
Monthly cost of pacemaker implantation	13,894	10,420–17,367	Gamma	Doble et al, 2013[39]
Outpatient visit costs for TAVI	264	198–325	Gamma	Reynolds et al, 2016[54]
Outpatient visit costs for SAVR	210	158–263	Gamma	Reynolds et al, 2016[54]

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Procedure-related costs and procedure-related adverse-event costs were obtained from Li et al.[56] Costs were based on a field evaluation of the use of TAVI in Ontario conducted since 2007. The Cardiac Care Network provided micro-costing data on all TAVI and SAVR procedures conducted during fiscal year 2012/13 from cardiac centres that participated in the Ontario Case Costing Initiative. The strength of using such cost data is that it truly reflects the financial burden in Ontario. More importantly, we incorporated these costs into the economic model using probabilistic sampling methods, which provided both means and 95% CIs that would be extremely useful for further calculations. Costs were reported in 2013 Canadian dollars; we converted them to 2015 Canadian dollars using purchasing power parity from the Bank of Canada.[59]

Treatment costs for patients who had an acute major stroke were taken from Mittmann et al.[57] In this 1-year prospective study, the authors collected the treatment costs (both index hospitalization and follow-up costs) for 232 patients who experienced ischemic stroke. The authors calculated the initial hospitalization costs and monthly follow-up costs associated with a major stroke event based on study cost data. In particular, the authors categorized hospitalization costs using averages for 0 to 3 months, 4 to 6 months, and 7 to 12 months. For follow-up costs of major stroke, we assumed the monthly cost in the first year to be the average of costs between 4 and 12 months. We assumed the monthly follow-up costs for the second year to be the average follow-up costs incurred in months 7 to 12. Costs from Mittmann et al[57]

were reported in 2009 Canadian dollars; we converted these to 2015 Canadian dollars using purchasing power parity from the Bank of Canada.[59]

We used various sources to obtain adverse-event costs. We took data for treatment costs related to major vascular complications and pacemaker implantation from Doble et al.[39] Costs from Doble et al[39] were reported in 2011 Canadian dollars; we converted them to 2015 Canadian dollars using purchasing power parity from the Bank of Canada.[59]

We took treatment costs for bleeding (life-threatening or disability) from Singh et al.[58] Costs from Singh et al[58] were reported in 2012 Canadian dollars; we converted them to 2015 Canadian dollars using purchasing power parity from the Bank of Canada.[59]

For the current analysis, we divided all costs into monthly costs.

Analysis

The primary outcomes of the base-case analysis were ICERs comparing TAVI with SAVR. We calculated the ICERs by taking the difference between TAVI and SAVR in expected costs, divided by the difference in expected QALYs produced by these two interventions.

We assessed the variability and uncertainty of model parameters by conducting one-way and probabilistic sensitivity analyses, as well as scenario analyses.

For the one-way sensitivity analyses, we varied model variables over plausible ranges and examined the impact this would have on the ICERs.

To determine the impact of simultaneously varying numerous variables within the assigned distributions, we conducted a probabilistic sensitivity analysis by running 1,000 simulations of the model parameters. We applied beta distributions to probabilities and utility parameters. We applied gamma distributions to cost parameters.

For scenario analyses, we explored the change in ICER values by applying a 2-year time horizon and a long-term hazard ratio comparing mortality between TAVI and SAVR. We used the value of 0.86 as reported by Reynolds et al[54] and effectiveness as life-years instead of QALYs.

Generalizability

The findings of this economic analysis cannot be generalized to all patients with severe aortic stenosis. They may, however, be used to guide decision-making about the specific patient populations addressed in the trials investigated by Health Quality Ontario.

Expert Consultation

We consulted experts whenever additional evidence was needed.

Results

Base-Case Analysis

Table 17 shows the results of the base-case analysis.

Table 17: Results of the Base-Case Analysis

Strategy	Average Total Cost, $		Incremental Cost,[a] $	Average Total Effect		Incremental Effect[b]	ICER[c]
	TAVI	SAVR		TAVI	SAVR		
Base case	73,594	64,183	9,412	2.448	2.267	0.181	51,988
95% Lower limit	73,711	63,998	—	2.4473	2.2701	—	—
95% Upper limit	73,477	64,368	—	2.4488	2.2639	—	—

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]Incremental cost = average cost (TAVI) – average cost (SAVR).
[b]Incremental effect = average total effect (TAVI) – average total effect (SAVR).
[c]ICER = incremental cost/incremental effect

Sensitivity Analysis

One-Way Sensitivity Analysis

Figure 25 presents the results of the one-way sensitivity analysis. The model was most sensitive to episode costs of both TAVI and SAVR, the monthly follow-up costs of major stroke in the first year, and the monthly follow-up costs of major stroke in the second year.

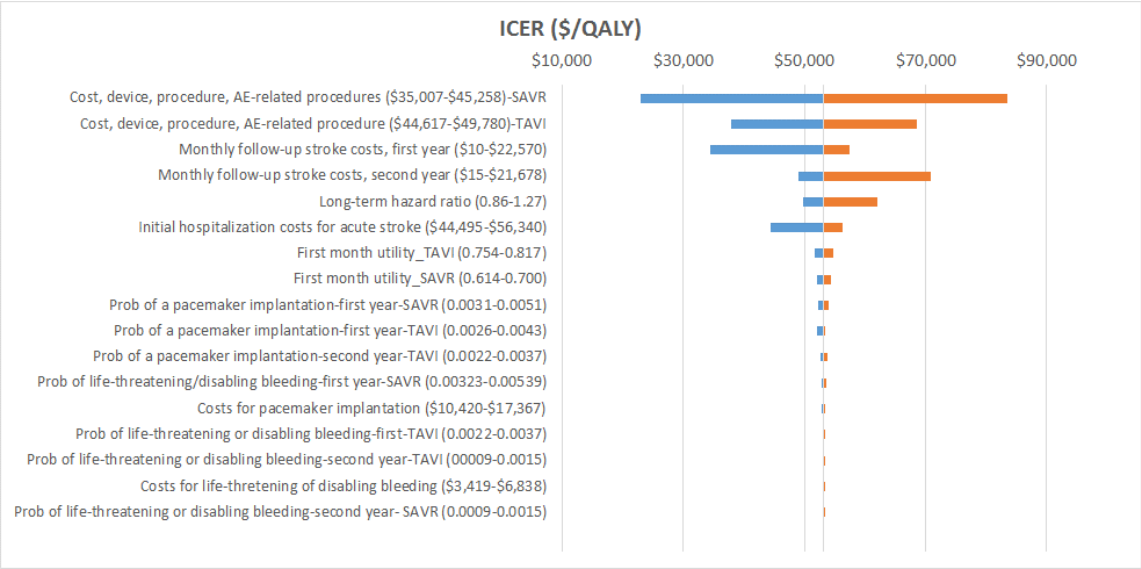

Figure 25: One-Way Sensitivity Analysis, TAVI vs. SAVR[a]

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]X-axis represents range of ICERs when base-case values are varied (ranges shown in parentheses). Vertical line represents the ICER for the TAVI system ($51,988 per QALY gained).

Probabilistic Sensitivity Analysis

We ran 1,000 simulations of the decision-analytic model comparing TAVI with SAVR, using random draws of all model parameters within the assigned distributions. Figure 26 presents the results. Assuming a willingness-to-pay threshold of $50,000 per QALY, the probability that TAVI would be cost-effective was 47%. At a willingness-to-pay threshold of $100,000 per QALY, the probability that TAVI would be cost-effective was 92%.

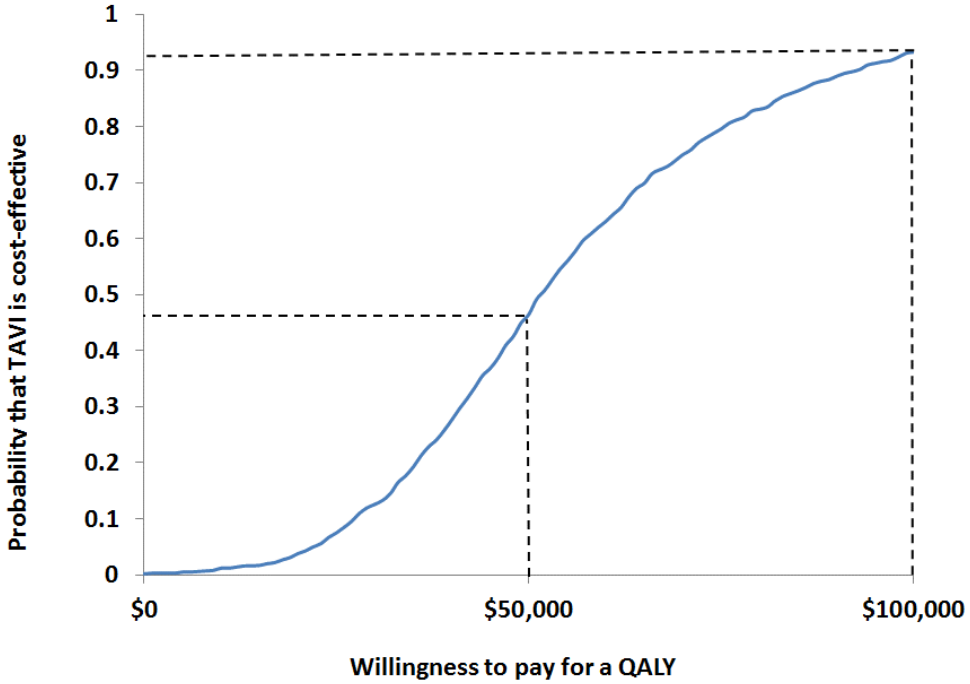

Figure 26: Cost-Effectiveness Acceptability Curve, TAVI vs. SAVR

Abbreviation: QALY, quality-adjusted life-year; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Scenario Analysis

Table 18 presents the results of the scenario analysis.

Table 18: Results of the Scenario Analysis

Strategy	Average Total Cost, $		Incremental Cost,[a] $	Average Total Effect		Incremental Effect[b]	ICER[c]
	TAVI	SAVR		TAVI	SAVR		
2-year time horizon	66,232	56,527	9,704	1.26	1.11	0.15	64,830
Long-term hazard ratio = 0.86	73,654	64,238	9,415	2.46	2.26	0.2	46,972
Effectiveness = life-year	73594	64,183	9,412	3.24	3.05	0.19	49,997

Abbreviations: ICER, incremental cost-effectiveness ratio; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Limitations

There were several limitations to the analysis. First, clinical data were based on a 2-year follow-up study. Further, we used generic health utility data that were available for only up to 1 year. Longer follow-up data would have provided an opportunity to consolidate the results of our analysis.

Discussion and Conclusions

We investigated the cost-effectiveness of TAVI compared with SAVR for patients with severe aortic stenosis who are at high surgical risk. Comparing with SAVR, TAVI would cost $51,988 per QALY gained. Sensitivity analyses showed that the results were robust to the changes in the model parameters were robust.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to determine the estimated cost burden of TAVI implantation over the next 5 years. All costs are reported in 2015 Canadian dollars.

Objectives

The objective of this study was to determine the budget impact of implementing TAVI over the next 5 years from the perspective of the Ontario Ministry of Health and Long-Term Care.

Methods

Target Population

The target population was patients with severe aortic stenosis who were at high surgical risk.

Resource

In 2015, 643 TAVI procedures were done in Ontario,[60] and we modelled under the assumption that the rate of TAVI procedures per 1 million population in Ontario would reach 61.23, equivalent to the rate in British Columbia. Table 19 shows the number of TAVI procedures per 1 million population across the provinces of Canada. We applied a rate of 61.23 TAVI procedures per 1 million population to estimate the total number of TAVI procedures to be performed in Ontario from 2016 onward. We assumed that this rate would remain constant between 2016 and 2020.

Table 19: TAVI Procedures Performed Across Canada, April 2013 to March 2014

	British Columbia	Alberta	Manitoba	Ontario	Quebec	New Brunswick	Nova Scotia
Total TAVI procedures	284	81	21	396	294	36	24
TAVI procedures/million	61.23	19.66	16.40	28.95	35.79	47.71	25.47

Abbreviation: TAVI, transcatheter aortic valve implantation.
Source: Dr. Wijeysundera, personal communication, March 4, 2016.

Table 20 shows the Ontario population forecast for the next 5 years.

Table 20: Estimated Ontario Population, 2016 to 2020

	2016	2017	2018	2019	2020
Population	13,930,021	14,069,321	14,210,014	14,352,115	14,495,635

Source: Statistics Canada.[61]

Table 21 shows the estimated number of expected TAVI procedures over the next 5 years.

Table 21: Number of Patients Expected to Receive TAVI in Ontario, 2016 to 2020

	Patients per Year Post-implant					
Year	Year 1	Year 2	Year 3	Year 4	Year 5	Total Patients, N
2016	853	—	—	—	—	853
2017	861	853	—	—	—	1,714
2018	870	861	853	—	—	2,584
2019	879	870	861	853	—	3,463
2020	888	879	870	861	853	4,351

Abbreviation: TAVI, transcatheter aortic valve implantation.

Canadian Costs

All costs used in the budget impact analysis were Canada- and Ontario-specific. The episode costs for TAVI and SAVR were provided by the Cardiac Care Network as described above. Treatment costs for acute major stroke, follow-up costs for major stroke, and treatment costs for TAVI- or SAVR-related adverse events were taken from the literature (Table 17). All costs are expressed in 2015 Canadian dollars.

We calculated the budget impact based on the estimated number of TAVI procedures to be performed in Ontario over the next 5 years. We used the episode cost of TAVI (the cost of the CoreValve device, the procedure cost, and the treatment cost of procedure-related adverse events), treatment costs for major stroke, and treatment costs for adverse events post-TAVI implantation as part of our analysis.

We obtained other costs from the primary economic analysis. Table 22 presents average costs per year in one patient who underwent either TAVI or SAVR.

Table 22: Average Cost per Patient With Severe Aortic Stenosis per Year[a]

	Year Post-Implant				
Therapy	Year 1	Year 2	Year 3	Year 4	Year 5
TAVI	$59,513	$7,802	$2,978	$2,810	$2,649
SAVR	$50,645	$6,841	$3,126	$2,979	$2,836

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

[a]In the first year, the following costs are incurred: episode cost of TAVI procedure, which includes (1) the cost of the device, the procedure and procedure-related adverse events; (2) the cost of treatment for major stroke (hospitalization and follow-up costs), if incurred; and (3) the cost of adverse events after the procedure, if incurred. In the subsequent years, the following costs are incurred: the cost of treatment of a new major stroke event, if incurred; the cost of follow-up for a major stroke event if it happened in the previous year; and treatment cost for adverse events, if incurred. All costs were calculated based on the proportion of patients who experienced no major stroke, or experienced a major stroke, and they accounted for mortality.

Results

Base-Case Analysis

The expected budget impact of adopting TAVI for the next 5 years would range between $7.6 million and $8.3 million per year (Table 23). In 2016, the net budget impact would be 7.6 million.

In 2017, the net budget impact would be the total of the net budget impact for 2016 and 2017. We performed similar calculations for 2018, 2019, and 2020. Notably, from 2018 onward, we found that there would be cost savings if TAVI were implemented in patients with severe aortic stenosis at high surgical risk.

Table 23: Budget Impact of Adopting TAVI in Ontario, 2016 to 2020

		Cost per Year Post-implant, $					
Year	Strategy	Year 1	Year 2	Year 3	Year 4	Year 5	Total, $
2016	TAVI	50,761,147	—	—	—	—	50,761,147
	SAVR	43,196,525	—	—	—	—	43,196,525
	Net budget impact	**7,564,622**	—	—	—	—	**7,564,622**
2017	TAVI	51,268,758	6,654,742	—	—	—	57,923,500
	SAVR	43,628,490	5,835,325	—	—	—	49,463,815
	Net budget impact	**7,640,268**	**819,417**	—	—	—	**8,459,685**
2018	TAVI	51,781,446	6,721,289	2,540,270	—	—	61,043,005
	SAVR	44,064,775	5,893,679	2,666,441	—	—	52,624,894
	Net budget impact	**7,716,671**	**827,611**	**–126,171**	—	—	**8,418,111**
2019	TAVI	52,299,260	6,788,502	2,565,673	2,396,322	—	64,049,757
	SAVR	44,505,423	5,952,615	2,693,105	2,541,128	—	55,692,271
	Net budget impact	**7,793,837**	**835,887**	**–127,433**	**–144,806**	—	**8,357,486**
2020	TAVI	52,847,976	6,928,323	2,644,702	2,494,836	2,351,967	67,267,805
	SAVR	44,972,367	6,075,220	2,776,060	2,645,595	2,517,949	58,987,192
	Net budget impact	**7,875,609**	**853,103**	**–131,358**	**–150,759**	**–165,983**	**8,280,613**

Abbreviations: SAVR, surgical aortic valve implantation; TAVI, transcatheter aortic valve implantation.
Note: Numbers may appear inexact due to rounding.

Discussion

Over the next 5 years (2016–2020), publicly funding TAVI for patients with severe aortic stenosis would result in additional costs of $7.6 million to $8.3 million per year. This finding includes potential savings of $126,171 to $165,983 from year 3 onward. Cost savings are expected to decrease over time as more individuals undergo the TAVI procedure and the number of individuals with a TAVI device rises.

The number of TAVI procedures performed in Ontario is an estimated 28.95 per 1 million population.[60] However, we calculated the net budget impact based on the number of TAVI procedures performed in British Columbia (61.23 per 1 million population),[60] reflective of the Canadian jurisdiction with the highest rate of TAVI procedures. Therefore, the net budget impact may be an overestimate for Ontario.

It is important to note that our analysis does not model a scenario in which all high-risk patients with severe aortic stenosis in Ontario receive a TAVI implant; the net budget impact for such a scenario would likely be higher. Within the scope of the present study, we aimed to provide a feasible scenario using rates from the jurisdiction with the highest rate of TAVI implantation in

Canada. Implementation considerations for TAVI include hospital capacity and infrastructure requirements, as well as the process for delivery to preclude long wait times for eligible patients.

Conclusions

Overall, our analysis suggests that if TAVI were publicly funded in patients with severe aortic stenosis at high surgical risk, the budget impact would be between $7.6 million and $8.3 million per year over the next 5 years (2016–2020).

ABBREVIATIONS

AMD	Adjusted mean difference
BAV	Balloon aortic valvuloplasty
CI	Confidence interval
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
NYHA	New York Heart Association
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QALY	Quality-adjusted life-year
SAVR	Surgical aortic valve replacement
SF-12	12-item Short Form questionnaire
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation

GLOSSARY

All-cause mortality	All deaths in a particular group without concern for the cause.
Aortic valve stenosis	A narrowing of the aortic valve, which controls the flow of blood between the heart's left ventricle and the primary artery (the aorta) exiting the heart.
Cardiovascular mortality	Death resulting from a problem in the heart or blood vessels.
Cohort	A group of individuals who share a common characteristic and who are part of a clinical trial or study.
Incremental cost-effectiveness ratio (ICER)	Determines "a unit of benefit" for an intervention by dividing the incremental cost by the incremental effectiveness. The incremental cost is the difference between the cost of the treatment under study and an alternative treatment. The incremental effectiveness is usually measured as additional years of life or as "quality-adjusted life-years"
Kaplan-Meier	A method to estimate the fraction of patients living for a particular span of time after a treatment.
Markov model	A type of modelling that measures the health state of a patient over the course of treatment. A patient may stay in one health state or move from one health state to another, depending on the effect of the treatment and the progression of the disease.
Quality-adjusted life-year (QALY)	A measurement that takes into account both the number of years gained by a patient from a procedure and the quality of those extra years (ability to function, freedom from pain, etc.). One QALY is expressed as a number between zero (no benefit) and one (perfect health). The QALY is commonly used as an outcome measure in cost–utility analyses.
Randomized controlled trial	A type of study in which subjects are assigned randomly into different groups, with one group receiving the treatment under study and the other group(s) receiving a different treatment or a placebo (no treatment) in order to determine the effectiveness of one approach compared with the other.

APPENDICES

Appendix 1: Literature Search Strategies

Search Strategy for the Clinical Evidence Review

Literature Search – TAVI

Search requested by: Shayan Sehatzadeh
Search date: September 30, 2015
Librarians: Corinne Holubowich
Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <3rd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 39>, All Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

#	Searches	Results
1	exp Aortic Valve Stenosis/	45048
2	((supravalvular or subvalvular or aort*) adj2 stenos?s).ti,ab.	35594
3	or/1-2	63767
4	Heart Valve Prosthesis Implantation/	25899
5	exp Heart Valve Prosthesis/	59222
6	(((aorta or aortic) adj2 (replace* or implant* or prosthe* or bioprosthe* or transplant*)) or avr).tw.	50800
7	or/4-6	107185
8	(transcatheter* or trans-catheter* or transfemoral or trans-femoral or transapical or trans-apical or percutaneous).tw.	298945
9	exp Surgical Procedures, Minimally Invasive/	447042
10	(minimal* adj3 (surgery or surgeries or surgical or procedure* or invasive)).tw.	116422
11	or/8-10	765541
12	7 and 11	18249
13	Transcatheter aortic valve implantation/	8455
14	(core-valve or corevalve or Cribier Edwards or Edwards valve* or Edwards Sapien or Sapien XT or Sapien 3 or Portico or Lotus or Evolut R or (transcatheter adj (heart or aortic) adj valve adj2 (replace* or implant*)) or TAVI or TAVR).tw.	17191
15	or/12-14	25185
16	3 and 15	9378
17	Meta-Analysis/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/	210519
18	Meta Analysis.pt.	60866
19	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw.	486314

20	(meta analy* or metaanaly* or health technolog* assess*).mp.	315567
21	Clinical Trials as Topic/ or Randomized Controlled Trials as Topic/	432485
22	(randomized controlled trial or controlled clinical trial).pt.	933021
23	trial.ti.	479103
24	(randomi#ed or randomly or RCT$1 or placebo* or sham).tw.	2225905
25	or/17-24	3341673
26	exp Animals/ not (exp Animals/ and Humans/)	9130432
27	25 not 26	2975802
28	16 and 27	1052
29	Case Reports/ or congresses.pt.	1840122
30	28 not 29	1046
31	30 use pmoz	396
32	16 use cctr,coch,dare,clhta,cleed	172
33	or/31-32	568
34	limit 33 to (english language and yr="2011 -Current") [Limit not valid in CDSR,DARE; records were retained]	451
35	exp aorta valve stenosis/	12332
36	((supravalvular or subvalvular or aort*) adj2 stenos?s).ti,ab.	35594
37	or/35-36	41383
38	aorta valve replacement/	15778
39	exp aorta valve prosthesis/	4917
40	(((aorta or aortic) adj2 (replace* or implant* or prosthe* or bioprosthe* or transplant*)) or avr).tw.	50800
41	or/38-40	57155
42	(transcatheter* or trans-catheter* or transfemoral or trans-femoral or transapical or trans-apical or percutaneous).tw.	298945
43	exp minimally invasive surgery/	445320
44	(minimal* adj3 (surgery or surgeries or surgical or procedure* or invasive)).tw.	116422
45	or/42-44	763980
46	41 and 45	15077
47	transcatheter aortic valve implantation/	8455
48	(core-valve or corevalve or Cribier Edwards or Edwards valve* or Edwards Sapien or Sapien XT or Sapien 3 or Portico or Lotus or Evolut R or (transcatheter adj (heart or aortic) adj valve adj2 (replace* or implant*)) or TAVI or TAVR).tw.	17191
49	or/46-48	22287
50	37 and 49	7790
51	Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/	199702
52	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw.	486314
53	(meta analy* or metaanaly* or health technolog* assess*).mp.	315567
54	exp "controlled clinical trial (topic)"/	86666
55	randomized controlled trial/ or controlled clinical trial/	1021271

56	trial.ti.	479103
57	(randomi#ed or randomly or RCT$1 or placebo* or sham).tw.	2225905
58	or/51-57	3206603
59	(exp animal/ or nonhuman/) not exp human/	9484953
60	58 not 59	2909809
61	50 and 60	978
62	Case Report/ or conference abstract.pt.	5721661
63	61 not 62	754
64	limit 63 to (english language and yr="2011 -Current") [Limit not valid in CDSR,DARE; records were retained]	610
65	64 use emez	326
66	34 or 65	777
67	66 use pmoz	305
68	66 use emez	326
69	66 use cctr	99
70	66 use coch	3
71	66 use dare	9
72	66 use clhta	18
73	66 use cleed	17
74	remove duplicates from 66	493

Search Strategy for the Economic Review

Literature Search – TAVI Update – Economic Results

Search requested by: Hong-Anh Tu
Search date: Oct 2, 2015
Librarians: Corinne Holubowich
Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <3rd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 39>, All Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

#	Searches	Results
1	exp Aortic Valve Stenosis/	45062
2	((supravalvular or subvalvular or aort*) adj2 stenos?s).ti,ab.	35596
3	or/1-2	63781
4	Heart Valve Prosthesis Implantation/	25913
5	exp Heart Valve Prosthesis/	59237
6	(((aorta or aortic) adj2 (replace* or implant* or prosthe* or bioprosthe* or transplant*)) or avr).tw.	50800

7	or/4-6	107200
8	(transcatheter* or trans-catheter* or transfemoral or trans-femoral or transapical or trans-apical or percutaneous).tw.	298939
9	exp Surgical Procedures, Minimally Invasive/	447293
10	(minimal* adj3 (surgery or surgeries or surgical or procedure* or invasive)).tw.	116405
11	or/8-10	765722
12	7 and 11	18255
13	Transcatheter aortic valve implantation/	8466
14	(core-valve or corevalve or Cribier Edwards or Edwards valve* or Edwards Sapien or Sapien XT or Sapien 3 or Portico or Lotus or Evolut R or (transcatheter adj (heart or aortic) adj valve adj2 (replace* or implant*)) or TAVI or TAVR).tw.	17192
15	or/12-14	25192
16	3 and 15	9385
17	economics/	248618
18	economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/	704317
19	economics.fs.	372496
20	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw.	644554
21	exp "costs and cost analysis"/	490427
22	cost*.ti.	221316
23	cost effective*.tw.	231805
24	(cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab.	144986
25	models, economic/	128867
26	markov chains/ or monte carlo method/	114768
27	(decision adj1 (tree* or analy* or model*)).tw.	31430
28	(markov or markow or monte carlo).tw.	93451
29	quality-adjusted life years/	25185
30	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw.	45467
31	((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw.	89307
32	or/17-31	2172813
33	16 and 32	404
34	33 use pmoz,cctr,coch,dare,clhta	134
35	16 use cleed	18
36	or/34-35	152
37	limit 36 to (english language and yr="2011 -Current") [Limit not valid in CDSR,DARE; records were retained]	133
38	exp aorta valve stenosis/	12332
39	((supravalvular or subvalvular or aort*) adj2 stenos?s).ti,ab.	35596
40	or/38-39	41385
41	aorta valve replacement/	15778
42	exp aorta valve prosthesis/	4917
43	(((aorta or aortic) adj2 (replace* or implant* or prosthe* or bioprosthe* or transplant*)) or	50800

	avr).tw.	
44	or/41-43	57155
45	(transcatheter* or trans-catheter* or transfemoral or trans-femoral or transapical or trans-apical or percutaneous).tw.	298939
46	exp minimally invasive surgery/	445571
47	(minimal* adj3 (surgery or surgeries or surgical or procedure* or invasive)).tw.	116405
48	or/45-47	764161
49	44 and 48	15079
50	transcatheter aortic valve implantation/	8466
51	(core-valve or corevalve or Cribier Edwards or Edwards valve* or Edwards Sapien or Sapien XT or Sapien 3 or Portico or Lotus or Evolut R or (transcatheter adj (heart or aortic) adj valve adj2 (replace* or implant*)) or TAVI or TAVR).tw.	17192
52	or/49-51	22290
53	40 and 52	7788
54	Economics/	248618
55	Health Economics/ or exp Pharmacoeconomics/	210203
56	Economic Aspect/ or exp Economic Evaluation/	378554
57	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw.	644554
58	exp "Cost"/	490427
59	cost*.ti.	221316
60	cost effective*.tw.	231805
61	(cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab.	144986
62	Monte Carlo Method/	48160
63	(decision adj1 (tree* or analy* or model*)).tw.	31430
64	(markov or markow or monte carlo).tw.	93451
65	Quality-Adjusted Life Years/	25185
66	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw.	45467
67	((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw.	89307
68	or/54-67	1779025
69	53 and 68	330
70	limit 69 to (english language and yr="2011 -Current") [Limit not valid in CDSR,DARE; records were retained]	289
71	70 use emez	198
72	37 or 71	331
73	72 use pmoz	93
74	72 use emez	198
75	72 use cctr	9
76	72 use coch	1
77	72 use dare	1
78	72 use clhta	12
79	72 use cleed	17
80	remove duplicates from 72	262

Appendix 2: Evidence Quality Assessment

Our first consideration was study design; we started with the assumption that RCTs are high quality, whereas observational studies are low quality. We then took into account five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias. Limitations in these areas resulted in downgrading the quality of evidence. Finally, we considered three main factors that may raise the quality of evidence: the large magnitude of effect, the dose-response gradient, and any residual confounding factors.[17] For more detailed information, please refer to the latest series of GRADE articles.[17]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	We are very confident that the true prognosis (probability of future events) lies close to that of the estimate
Moderate	We are moderately confident that the true prognosis (probability of future events) is likely to be close to the estimate, but there is a possibility that it is substantially different
Low	Our confidence in the estimate is limited: the true prognosis (probability of future events) may be substantially different from the estimate
Very Low	We have very little confidence in the estimate: the true prognosis (probability of future events) is likely to be substantially different from the estimate

Table A1: GRADE Evidence Profile for Comparison of TAVI and SAVR in the PARTNER Trial, Cohort A

Number of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Number of Patients	Relative Effect	GRADE
NYHA Functional Class								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	699	No difference between groups up to 5 years	⊕⊕⊕ Moderate
Quality of Life								
1 RCT	Serious limitations (–2)[a]	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	NA	No difference between groups at 1 year; no further follow-up	⊕⊕ Low
Mortality								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	699	No significant difference between TAVI and SAVR up to 5 years	⊕⊕⊕ Moderate
Paravalvular Aortic Regurgitation								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	Serious limitations	Undetected	699	Significantly higher in TAVI (moderate/severe, 6.9% vs.0.9%, mild 38.6% vs. 6.3% at 2 years)	⊕⊕⊕ Moderate
Major Stroke								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	699	Two times higher in TAVI than SAVR at 1 or 2 years	⊕⊕⊕ Moderate
Major Vascular Complications								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	699	Significantly higher in TAVI (11.6% vs. 3.8% at 2 years)	⊕⊕⊕ Moderate
Major Bleeding								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	699	Significantly higher in SAVR (29.5% vs.19% at 2 years)	⊕⊕⊕ Moderate
Need for Pacemaker Implantation								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	699	No difference between groups	⊕⊕⊕ Moderate

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]High rate of missing data at baseline (10%) and follow-up (approximately 20% of those who were eligible for follow-up). The assessments were unblinded.

Table A2: GRADE Evidence Profile for Comparison of TAVI and SAVR in the US CoreValve Trial

Number of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Number of Patients	Relative Effect	GRADE
NYHA Functional Class								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	795	No difference between groups up to 2 years	⊕⊕⊕ Moderate
Quality of Life								
1 RCT	Serious limitations (–2)[a]	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	NA	No difference between groups at 1 year; no further follow-up	⊕⊕ Low
Mortality								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	795	No difference in cardiac mortality but significant difference in all-cause mortality at 2 years (TAVI 22.2%; SAVR 28.6%)	⊕⊕⊕ Moderate
Paravalvular Aortic Regurgitation								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	795	Significantly higher in TAVI (moderate/severe, 6.1 % vs.0.6%; mild, 29.9% vs. 7.2% at 2 years)	⊕⊕⊕ Moderate
Major Stroke								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	795	No difference between groups at 2 years due to unusually high rate of stroke in SAVR group (not explained)	⊕⊕⊕ Moderate
Major Vascular Complications								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	795	Significantly higher in TAVI (7.1% vs. 2.0% at 2 years)	⊕⊕⊕ Moderate
Major Bleeding								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	795	No difference between groups at 2 years	⊕⊕⊕ Moderate
Need for Pacemaker Implantation								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	795	Significantly higher in TAVI (25.8% vs. 12.8% at 2 years)	⊕⊕⊕ Moderate

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]High rate of missing data: 11% had missing data at baseline, and 1 year follow-up was available for only 74% of those eligible for follow-up.
The assessments were unblinded.

Table A3: GRADE Evidence Profile for Comparison of TAVI and SAVR in the NOTION Trial

Number of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Number of Patients	Relative Effect	GRADE
NYHA Functional Class								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	280	No significant difference between groups up to 1 year. However, patients who underwent TAVI had significantly more dyspnea than the SAVR group at 1 year (P = .01)	⊕⊕⊕ Moderate
Quality of Life								
Not reported								Unknown
Mortality								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	280	No difference between TAVI and SAVR at 1 year	⊕⊕⊕ Moderate
Paravalvular Aortic Regurgitation								
Not reported								Unknown
Major Stroke								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	280	No difference between TAVI and SAVR at 1 year	⊕⊕⊕ Moderate
Major Vascular Complications								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	280	Higher in TAVI than SAVR (5.6% vs.1.5% at 1 year)	⊕⊕⊕ Moderate
Major Bleeding								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	280	Significantly higher in SAVR (20.9% vs.11.3% at 1 year)	⊕⊕⊕ Moderate
Need for Pacemaker Implantation								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	280	Significantly higher in TAVI (38% vs. 2.4% at 2 years)	⊕⊕⊕ Moderate

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Table A4: GRADE Evidence Profile for Comparison of TAVI and SAVR in the PARTNER Trial, Cohort B

Number of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Number of Patients	Relative Effect	GRADE
NYHA Functional Class								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	358	At 1 year, 86% of transfemoral TAVI survivors and 60% of BAV survivors had a NYHA functional class of I or II	⊕⊕⊕ Moderate
Quality of Life								
1 RCT	Serious limitations (–2)[a]	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	NA	Significant difference between groups at 1 year; no further follow-up	⊕⊕ Low
Mortality								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	358	Significantly lower in TAVI than in BAV up to 5 years	⊕⊕⊕ Moderate
Paravalvular Aortic Regurgitation								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	358	Higher in TAVI (moderate/severe, 4.5 % vs. 0% at 2 years)	⊕⊕⊕ Moderate
Major Stroke								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	358	More than two times higher in TAVI than in BAV at 2 years (10.1% vs.3.9%)	⊕⊕⊕ Moderate
Major Vascular Complications								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	358	Significantly higher in TAVI (17.4% vs.2.8% at 3 years)	⊕⊕⊕ Moderate
Major Bleeding								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	358	No difference between groups	⊕⊕⊕ Moderate
Need for Pacemaker Implantation								
1 RCT	No serious limitations	Undetermined (1 RCT only)	No serious limitations	No serious limitations	Undetected	358	No difference between groups	⊕⊕⊕ Moderate

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]High rate of missing data: 19% of survivors at 6 months and 16% of survivors at 1 year did not complete the questionnaire. The assessments were unblended.

REFERENCES

(1) Brennan JM, Edwards FH, Zhao Y, O'Brien SM, Douglas PS, Peterson ED. Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. Circulation. 2012;126(13):1621-9.

(2) Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002-12.

(3) Walther T, Blumenstein J, van Linden A, Kempfert J. Contemporary management of aortic stenosis: surgical aortic valve replacement remains the gold standard. Heart. 2012;98 Suppl 4:iv23-9.

(4) Bakaeen FG, Chu D, Ratcliffe M, Gopaldas RR, Blaustein AS, Venkat R, et al. Severe aortic stenosis in a veteran population: treatment considerations and survival. Ann Thorac Surg. 2010;89(2):453-8.

(5) Chitsaz S, Jaussaud N, Chau E, Yan KS, Azadani AN, Ratcliffe MB, et al. Operative risks and survival in veterans with severe aortic stenosis: surgery versus medical therapy. Ann Thorac Surg. 2011;92(3):866-72.

(6) Varadarajan P, Kapoor N, Bansal RC, Pai RG. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged > or =80 years. Eur J Cardiothorac Surg. 2006;30(5):722-7.

(7) Webb J, Rodes-Cabau J, Fremes S, Pibarot P, Ruel M, Ibrahim R, et al. Transcatheter aortic valve implantation: a Canadian Cardiovascular Society position statement. Can J Cardiol. 2012;28(5):520-8.

(8) Kapadia S, Stewart WJ, Anderson WN, Babaliaros V, Feldman T, Cohen DJ, et al. Outcomes of inoperable symptomatic aortic stenosis patients not undergoing aortic valve replacement: Insight into the impact of balloon aortic valvuloplasty from the PARTNER trial (Placement of AoRtic TraNscathetER Valve Trial). JACC Cardiovasc Interv. 2015;8(2):324-33.

(9) Wang A, Harrison JK, Bashore TM. Balloon aortic valvuloplasty. Prog Cardiovasc Dis. 1997;40(1):27-36.

(10) Otto CM, Mickel MC, Kennedy JW, Alderman EL, Bashore TM, Block PC, et al. Three-year outcome after balloon aortic valvuloplasty. Insights into prognosis of valvular aortic stenosis. Circulation. 1994;89(2):642-50.

(11) Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry. Circulation. 1991;84(6):2383-97.

(12) Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366(18):1686-95.

(13) Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med. 2012;366(18):1696-704.

(14) Sehatzadeh S, Doble B, Xie F, Blackhouse G, Campbell K, Kaulback K, et al. Transcatheter aortic valve implantation (TAVI) for treatment of aortic valve stenosis: an evidence update. Ont Health Technol Assess Ser [Internet]. 2013;13(1):1-40. Available from: http://www.hqontario.ca/Portals/0/Documents/evidence/reports/report-tavi-aortic-valve-stenosis-130516-en.pdf.

(15) Sehatzadeh S, Doble B, Xie F, Blackhouse G, Campbell K, Kaulback K, et al. Transcatheter aortic valve implantation (TAVI) for treatment of aortic valve stenosis: An evidence-based analysis (part B). Ont Health Technol Assess Ser. 2013;13(1).
(16) Masson JB, Kovac J, Schuler G, Ye J, Cheung A, Kapadia S, et al. Transcatheter aortic valve implantation: review of the nature, management, and avoidance of procedural complications. JACC Cardiovasc Interv. 2009;2(9):811-20.
(17) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.
(18) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12.
(19) Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-607.
(20) Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.
(21) Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;370(19):1790-8.
(22) Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. J Am Coll Cardiol. 2015;65(20):2184-94.
(23) Nielsen HHM, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ, et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: The STACCATO trial. EuroIntervention. 2012;8(3):383-9.
(24) Reynolds MR, Magnuson EA, Lei Y, Leon MB, Smith CR, Svensson LG, et al. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. Circulation. 2011;124(18):1964-72.
(25) Kapadia SR, Tuzcu EM, Makkar RR, Svensson LG, Agarwal S, Kodali S, et al. Long-term outcomes of inoperable patients with aortic stenosis randomly assigned to transcatheter aortic valve replacement or standard therapy. Circulation. 2014;130(17):1483-92.
(26) Svensson LG, Blackstone EH, Rajeswaran J, Brozzi N, Leon MB, Smith CR, et al. Comprehensive analysis of mortality among patients undergoing TAVR: results of the PARTNER trial. J Am Coll Cardiol. 2014;64(2):158-68.
(27) Douglas PS, Hahn RT, Pibarot P, Weissman NJ, Stewart WJ, Xu K, et al. Hemodynamic outcomes of transcatheter aortic valve replacement and medical management in severe, inoperable aortic stenosis: a longitudinal echocardiographic study of cohort B of the PARTNER trial. J Am Soc Echocardiogr. 2015;28(2):210-7.e1-9.
(28) Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2485-91.
(29) Miller DC, Blackstone EH, Mac KMJ, Svensson LG, Kodali SK, Kapadia S, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. J Thorac Cardiovasc Surg. 2012;143(4):832-43.e13.

(30) Reynolds MR, Magnuson EA, Wang K, Thourani VH, Williams M, Zajarias A, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial (Cohort A). J Am Coll Cardiol. 2012;60(6):548-58.
(31) Hahn RT, Pibarot P, Stewart WJ, Weissman NJ, Gopalakrishnan D, Keane MG, et al. Comparison of transcatheter and surgical aortic valve replacement in severe aortic stenosis: A longitudinal study of echocardiography parameters in cohort a of the PARTNER trial (Placement of aortic transcatheter valves). J Am Coll Cardiol. 2013;61(25):2514-21.
(32) Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385(9986):2477-84.
(33) Arnold SV, Reynolds MR, Wang K, Magnuson EA, Baron SJ, Chinnakondepalli KM, et al. Health status after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis at increased surgical risk results from the CoreValve US Pivotal Trial. JACC Cardiovasc Interv. 2015;8(9):1207-17.
(34) Reardon MJ, Adams DH, Kleiman NS, Yakubov SJ, Coselli JS, Deeb GM, et al. 2-year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. J Am Coll Cardiol. 2015;66(2):113-21.
(35) The Criteria Committee of the New York Heart Association. Diseases of the heart and blood vessels: Nomenclature and criteria for diagnosis. Boston (MA): Little Brown; 1964.
(36) Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245-55.
(37) Wyrwich KW, Spertus JA, Kroenke K, Tierney WM, Babu AN, Wolinsky FD. Clinically important differences in health status for patients with heart disease: an expert consensus panel report. Am Heart J. 2004;147(4):615-22.
(38) Brecker S, Mealing S, Padhiar A, Eaton J, Sculpher M, Busca R, et al. Cost-utility of transcatheter aortic valve implantation for inoperable patients with severe aortic stenosis treated by medical management: a UK cost-utility analysis based on patient-level data from the ADVANCE study. Open Heart. 2014;1(1):e000155.
(39) Doble B, Blackhouse G, Goeree R, Xie F. Cost-effectiveness of the Edwards SAPIEN transcatheter heart valve compared with standard management and surgical aortic valve replacement in patients with severe symptomatic aortic stenosis: a Canadian perspective. J Thorac Cardiovasc Surg. 2013;146(1):52-60.e3.
(40) Fairbairn TA, Meads DM, Hulme C, Mather AN, Plein S, Blackman DJ, et al. The cost-effectiveness of transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis at high operative risk. Heart. 2013;99(13):914-20.
(41) Gada H, Kapadia SR, Tuzcu EM, Svensson LG, Marwick TH. Markov model for selection of aortic valve replacement versus transcatheter aortic valve implantation (without replacement) in high-risk patients. Am J Cardiol. 2012;109(9):1326-33.
(42) Hancock-Howard RL, Feindel CM, Rodes-Cabau J, Webb JG, Thompson AK, Banz K. Cost effectiveness of transcatheter aortic valve replacement compared to medical management in inoperable patients with severe aortic stenosis: Canadian analysis based on the PARTNER Trial Cohort B findings. J Med Econ. 2013;16(4):566-74.
(43) Murphy A, Fenwick E, Toff WD, Neilson MP, Berry C, Uren N, et al. Transcatheter aortic valve implantation for severe aortic stenosis: the cost-effectiveness case for inoperable patients in the United Kingdom. Int J Technol Assess Health Care. 2013;29(1):12-9.

(44) Neyt M, Van Brabandt H, Devriese S, Van De Sande S. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. BMJ Open. 2012;2(3).
(45) Reynolds MR, Magnuson EA, Lei Y, Wang K, Vilain K, Li H, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). J Am Coll Cardiol. 2012;60(25):2683-92.
(46) Reynolds MR, Magnuson EA, Wang K, Lei Y, Vilain K, Walczak J, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (cohort B). Circulation. 2012;125(9):1102-9.
(47) Ribera A, Slof J, Andrea R, Falces C, Gutierrez E, Del Valle-Fernandez R, et al. Transfemoral transcatheter aortic valve replacement compared with surgical replacement in patients with severe aortic stenosis and comparable risk: cost-utility and its determinants. Int J Cardiol. 2015;182:321-8.
(48) Watt M, Mealing S, Eaton J, Piazza N, Moat N, Brasseur P, et al. Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. Heart. 2012;98(5):370-6.
(49) Linke A, Wenaweser P, Gerckens U, Tamburino C, Bosmans J, Bleiziffer S, et al. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. Eur Heart J. 2014;35(38):2672-84.
(50) Gada H, Agarwal S, Marwick TH. Perspective on the cost-effectiveness of transapical aortic valve implantation in high-risk patients: outcomes of a decision-analytic model. Ann Cardiothorac Surg. 2012;1(2):145-55.
(51) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.
(52) Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: canada [Internet]. Ottawa: CADTH; 2006 [cited 2015 Sep 2]. Available from: https://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf
(53) Briggs A, Claxton K, Sculpher M. Further developments in decision analytic models for economic evaluation. In: Gray A, Briggs AH, editors. Decision modelling for health economic evaluation. Cambridge, UK: Oxford University Press; 2008. p. 45-76.
(54) Reynolds MR, Lei Y, Wang K, Chinnakondepalli K, Vilain KA, Magnuson EA, et al. Cost-effectiveness of transcatheter aortic valve replacement with a self-expanding prosthesis versus surgical aortic valve replacement. J Am Coll Cardiol. 2016;67(1):29-38.
(55) EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
(56) Li L, Braga V, Pardhan A, Lian D, Leeksma A, Walker J, et al. Predictors of costs in cardiac surgery and transcatheter aortic valve implantation (TAVI) procedures in Ontario [abstract]. Can J Cardiol. 2015;31(10):S83-4.
(57) Mittmann N, Seung SJ, Hill MD, Phillips SJ, Hachinski V, Cote R, et al. Impact of disability status on ischemic stroke costs in Canada in the first year. Can J Neurol Sci. 2012;39(6):793-800.
(58) Singh SM, Micieli A, Wijeysundera HC. Economic evaluation of percutaneous left atrial appendage occlusion, dabigatran, and warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. Circulation. 2013;127(24):2414-23.
(59) Bank of Canada [Internet]. Ottawa (ON): The Bank; 2016 [cited 2016 Feb 22]. Available from: http://www.bankofcanada.ca/rates/exchange/10-year-converter/

(60) Cardiac Care Network. Cardiac Care Network Annual Report 2013-2014 [Internet]. Toronto (ON): The Network; 2014 [cited 2016 Jul 6]. Available from: http://www.ccn.on.ca/ccn_public/uploadfiles/files/CCN_Annual_Report_2013_14.pdf

(61) Statistics Canada [Internet]. Ottawa (ON): Government of Canada; [updated 2016 May 03; cited 2016 May 11]. Available from: http://www.statcan.gc.ca/start-debut-eng.html

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We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

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We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

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We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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