Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Transcatheter Valve-in-Valve Implantation for Degenerated Mitral or Tricuspid Bioprosthetic Valves: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Heart valve disease can occur in any of the four valves of the heart (pulmonary, mitral, aortic, or tricuspid), and it can lead to heart failure. The most common treatment for heart valve disease is open-heart surgery to replace the damaged valve with an artificial one. However, a common type of artificial valve, called a bioprosthetic valve, lasts only about 10 to 15 years.

Transcatheter valve-in-valve implantation is a less invasive treatment for people whose first bioprosthetic valve is failing and who cannot have another surgery or are at high risk for a poor outcome from another open-heart surgery. With transcatheter valve-in-valve implantation, cardiologists insert a catheter (a tube) into a large vein and thread the new valve through the vein, up into the heart. The new valve is placed inside the old valve, and it pushes the old valve out of the way.

This health technology assessment looked at how safe and effective transcatheter valve-in-valve implantation is for adults with failing mitral or tricuspid bioprosthetic valves who cannot have surgery or are high-risk for surgery. It also looked at the budget impact of publicly funding transcatheter valve-in-valve implantation and at the experiences, preferences, and values of adults with failing mitral or tricuspid bioprosthetic valves.

What Did This Health Technology Assessment Find?

Adults who received transcatheter valve-in-valve implantation for failing mitral or tricuspid bioprosthetic valves experienced improvement in their heart failure symptoms after the procedure. One year after the procedure, most patients had survived.

We estimate that publicly funding transcatheter valve-in-valve implantation for failing mitral or tricuspid bioprosthetic valves could lead to a cost saving of $0.33 million over the next 5 years.

People with a failing bioprosthetic heart valve said that heart valve disease affected their quality of life. The people we spoke with liked the idea of transcatheter valve-in-valve implantation because it was less invasive and had a quick recovery time.

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Abstract

Background

Bioprosthetic valves used to treat mitral or tricuspid valve disease can be expected to deteriorate and eventually fail after 10 to 15 years. For patients who are considered inoperable or high-risk for surgery, medical management (i.e., drug therapy, the current standard of care in Ontario) does not significantly alter the course of valvular heart disease or improve degenerated bioprosthetic valves. An alternative for these patients is transcatheter mitral or tricuspid valve-in-valve implantation (TMViV or TTViV). We conducted a health technology assessment of transcatheter valve-in-valve implantation for adults with degenerated mitral or tricuspid bioprosthetic valves who are considered inoperable or high-risk for surgery, which included an evaluation of effectiveness, safety, the budget impact of publicly funding TMViV or TTViV, and patient preferences and values.

Methods

We leveraged a previously published systematic review, supplementing the work with two new registry studies identified during the development of this report. We assessed the risk of bias of each included study using the Downs and Black checklist and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. As the earlier systematic review did not identify any cost-effectiveness studies, we conducted a hand search of the grey literature using targeted websites to identify relevant cost-effectiveness studies. We analyzed the budget impact of publicly funding transcatheter valve-in-valve implantation for adults with degenerated mitral or tricuspid bioprostheses who are considered inoperable or high-risk for surgery in Ontario. To contextualize the potential value of TMViV and TTViV, we spoke with people who had experience with heart valve replacement or who were awaiting heart valve replacement.

Results

We included 19 studies in the clinical evidence review. No studies compared TMViV or TTViV to medical management (standard care). TMViV was associated with in-hospital, 30-day and 1-year mortality rates of 0% to 5%, 0% to 15%, and 14% to 27%, respectively (GRADE: Very low). TTViV was associated with 30-day and 1-year mortality rates of 0% to 3% and 0% to 14%, respectively (GRADE: Very low). Patients experienced functional improvement related to their heart failure symptoms after TMViV or TTViV. Compared to before the intervention, both TMViV and TTViV were associated with a decrease in the number of patients with New York Heart Association class III or IV symptoms in hospital and at 30-day follow-up (GRADE: Low). We identified no relevant cost-effectiveness studies from our targeted search. The annual budget impact of publicly funding TMViV and TTViV in Ontario over the next 5 years ranges from an additional $0.35 million in year 1 to a cost saving of $0.19 million in year 5, for a total cost saving of $0.33 million. The people we spoke to who had bioprosthetic heart valve failure reported the negative effects of valvular heart disease and described their positive perceptions of transcatheter valve-in-valve implantation. They valued the minimally invasive nature of transcatheter procedures and the quick recovery time.

Conclusions

TMViV or TTViV may reduce mortality, but the evidence is very uncertain. TMViV or TTViV may improve heart failure symptoms. We estimated that publicly funding TMViV and TTViV in Ontario would result in a cost saving of $0.33 million over the next 5 years. People with valvular heart disease reported their preference for a minimally invasive transcatheter procedure with a quick recovery time.

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Objective

This health technology assessment evaluates the effectiveness and safety of transcatheter valve-in-valve implantation for adults with degenerated mitral or tricuspid bioprosthetic valves. It also evaluates the budget impact of publicly funding transcatheter valve-in-valve implantation and the experiences, preferences, and values of people with degenerated mitral or tricuspid bioprosthetic valves.

Background

Health Condition

Valvular heart disease can occur in any of the four valves of the heart (pulmonary, mitral, aortic, or tricuspid) and can involve stenosis (stiffening of the valve), prolapse (shifting of the valve out of place), or regurgitation (leaking).[1] It can be congenital (developing at or before birth) or acquired (for example, because of age or an infection). Symptoms may vary according to the severity of the damage to the valve and its function, but may include chest pain or tightness, palpitations, or shortness of breath.[1]

Mitral valve disease is the second most common type of valvular heart disease (aortic stenosis is the most common).[2] Mitral valve prolapse is the most common cause in the Western world whereas rheumatic heart disease is the leading cause of mitral regurgitation elsewhere.[2]
Patients with severe tricuspid valve disease may present with right heart failure that is progressive and intractable (resistant to treatment). Isolated tricuspid regurgitation is associated with increased mortality, even in the absence of other cardiopulmonary comorbidities.[4]

Clinical Need and Target Population

The prevalence of valvular heart disease is about 2.5% in industrialized countries. Acute and chronic mitral regurgitation affect approximately 5 in 10,000 people.[2] Estimates of long-term survival vary in people with severe mitral regurgitation, from 27% to 95% at 5 years.[3,5] In a study of the natural history of mitral regurgitation, patients had excess mortality (6.3% yearly) compared to their expected survival.[6] High morbidity was also present: the 10-year incidence of atrial fibrillation was 30%, and the 10-year incidence of heart failure was 63%.[6] Also at 10 years, 90% of patients were dead or had undergone surgery, suggesting that surgery was almost unavoidable.[6] People with New York Heart Association (NYHA) functional class III or IV symptoms (severe heart failure symptoms) displayed considerable mortality (34% yearly) if they did not undergo surgery, but even those with class I or II symptoms (mild to moderate heart failure symptoms) had notable mortality (4.1% yearly).[6]

Nearly 1.6 million people in the United States have moderate to severe tricuspid regurgitation,[4] and severe tricuspid regurgitation is associated with a poor prognosis. The 1-year survival rates for people with moderate or severe tricuspid regurgitation range from 64% to 79%.[7] Five- and 10-year survival rates are 51.7% and 30.5%, respectively.[8]

To date, no options for medical management (drug therapies such as diuretics and anticoagulants) have substantially altered the course of valvular heart disease.[9] People with severe valve regurgitation usually undergo open-heart surgery; the valve is repaired if possible, but if this is not technically feasible it is replaced with a mechanical or bioprosthetic valve. Mechanical valves are more durable, but bioprosthetic heart valves are often favoured because of a lower risk of thrombotic and bleeding events and the desire to avoid anticoagulation.[10] However, within approximately 10 to 15 years, bioprosthetic tissue can be expected to deteriorate and eventually fail.[1]

Current Treatment Options

Reoperation has been the standard treatment for bioprosthetic valves that develop severe stenosis or regurgitation; however, repeat surgery may carry significant risks.[10] The Society of Thoracic Surgeons risk calculator predicts that an 80-year-old man with no comorbidities has an approximate mortality risk of 5% for aortic valve reoperation and 10% for mitral valve reoperation, as well as major morbidity risks of 20% and 23%, respectively.[10] These risks increase dramatically in the presence of comorbidities.[10,11] Surgical referral for tricuspid valve disease is limited by concerns about in-hospital mortality, which can be as high as 24%.[4] As a result, some people are considered inoperable or high-risk for open-heart valve replacement surgery. The current standard of care in Ontario for these people is medical management (i.e., drug therapy).

Because medical management does not significantly alter the course of valvular heart disease[9] or improve degenerated bioprosthetic valves, the alternative for those who are considered inoperable or high-risk for open-heart surgery (as determined by Society of Thoracic Surgeons risk score[12] and clinical judgment) is transcatheter valve-in-valve implantation.

Health Technology Under Review

Transcatheter mitral or tricuspid valve-in-valve implantation (TMViV or TTViV, respectively) is a less invasive alternative to conventional surgical valve replacement for people with degenerated bioprosthetic valves who are considered inoperable or high-risk for surgery.[1]

During TMViV, the valve can be delivered through the apex of the heart via direct left ventricular access (transapical access) or through the femoral vein and transseptal puncture to the mitral valve (transseptal access). The latter approach is preferred because it is less invasive. During TTViV, an interventional cardiologist and/or cardiac surgeon inserts a catheter (tube) through the femoral or jugular vein. In both TMViV and TTViV, the new bioprosthetic valve is compressed and advanced within a catheter through a vein until it reaches the degenerated bioprosthetic valve. A balloon, also delivery within the catheter, expands and secures the new valve inside the failing valve. The catheter is then removed and the secured new valve remains in place, effectively replacing the degenerated valve.[13]

Regulatory Information

The United States Food and Drug Administration approved use of the Edwards Sapien 3 transcatheter heart valve for TMViV procedures in 2017; it is indicated "for patients with symptomatic heart disease due to failure of a previously placed bioprosthetic aortic or mitral valve whose risk of death or severe complications from repeat surgery is high or greater."[14]

The Edwards Sapien 3 is licensed by Health Canada as a class IV device. The licensed indication is for TMViV in people who have degenerated bioprosthetic mitral valves and are considered inoperable or high-risk for surgery.[15] The Edwards Sapien 3 does not have a licensed indication for TTViV in people who have a degenerated bioprosthetic tricuspid valve and are considered inoperable or high-risk for surgery. At present, the Edwards Sapien 3 is used off-label for TTViV.

The National Institute for Health and Care Excellence (NICE) is expected to publish revised guidance on TMViV in 2021.[16] It will replace the older guidance issued on December 16, 2015, which stated:

> *The current evidence on the safety of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis shows the potential for serious complications. However, this is in patients for whom open surgical valve implantation is unsuitable, who have severe symptoms and a high risk of death. The evidence on efficacy shows generally good symptom relief in the short term, but is based on very small numbers of patients. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.*[17]

Ontario Context

Transcatheter valve-in-valve implantation for degenerated mitral or tricuspid bioprosthetic valves is currently performed in Ontario at seven cardiac centres that specialize in transcatheter valve implantation and have a mitral program (Harindra Wijeysundera, MD, email communication, February 26, 2021). The cost of the device is covered by philanthropic funds or hospital global budgets (CorHealth, phone communication, February 2021).

There is no Ministry of Health program funding for transcatheter valve-in-valve implantation for degenerated mitral or tricuspid bioprosthetic valves.

In Ontario, approximately 25 people per year may be candidates for TMViV and one to two people per year may be candidates for TTViV (Harindra Wijeysundera, MD, email communication, February 26, 2021).

Expert Consultation

We engaged with experts in the specialty area of interventional cardiology to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

Clinical Evidence

Research Question

What are the effectiveness and safety of transcatheter valve-in-valve implantation compared with medical management (standard care, i.e., drug therapy) for the treatment of adults with degenerated mitral or tricuspid bioprosthetic valves and who are considered inoperable or high-risk for surgery?

Methods

During initial scoping for this report, we identified a recent rapid response report (October 2020) conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) on transcatheter valve-in-valve implantation for degenerated mitral or tricuspid bioprosthetic valves.[1] In that systematic review, CADTH[1] undertook a literature search for reports limited to English-language documents published between January 1, 2015, and July 29, 2020. The review was broader in scope than the focus of this report, in that it included studies that compared transcatheter valve-in-valve implantation with surgery.

Our aim was to leverage the findings of CADTH's rapid response report, supplementing that work with two new registry studies[18,19] identified during the development of our report.

Clinical Literature Search Assessment

As part of the process to determine whether the CADTH rapid response report was appropriate to our purposes, we obtained the literature search from their information specialists.[1] We assessed the clinical literature search on March 1, 2021, and found that the search methods used were similar to our own in terms of databases searched, including Medline, Embase, the Cochrane Library, and the University of York Centre for Reviews and Dissemination databases. The study design filters, language limits, and grey literature search were also suitable for our review. The search terms were appropriate and focused, and they matched our clinical question and eligibility criteria. Because the CADTH search was conducted in July 2020, we determined that a search update would not be necessary, based on expert consultation and the expedited nature of this review.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies identified in the CADTH rapid response report[1] (published between January 1, 2015, and July 29, 2020); during the development of this health technology assessment, stakeholders identified two additional studies published after the CADTH review
- Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, nonrandomized studies (including single-arm studies)

PARTICIPANTS

- People over age 18 years with degenerated mitral or tricuspid bioprosthetic valves who were considered inoperable or high-risk for surgery

INTERVENTIONS

Interventions

The CADTH rapid response report[1] used the term "transcatheter valve-in-valve replacement using a transcatheter aortic valve"; for greater clarity, we used the following terms to describe the interventions evaluated in this health technology assessment:

- Transcatheter mitral valve-in-valve implantation (TMViV)
- Transcatheter tricuspid valve-in-valve implantation (TTViV)

Comparators

- Medical management/drug therapy
- Before and after TMViV or TTViV

The CADTH rapid response report[1] included surgery as a comparator, but because the present health technology assessment focused specifically on those who were considered inoperable or high-risk for surgery, we excluded surgery.

OUTCOME MEASURES

- Mortality
- Stroke
- Myocardial infarction
- New York Heart Association (NYHA) functional class (a classification that places people with heart failure in one of four categories based on how much they are limited during physical activity; class I is associated with no symptoms and class IV signifies severe physical limitations, with symptoms at rest)[20]
- Complications
- Hospital or intensive care unit length of stay
- Subanalysis of transcatheter access routes for TMViV, if reported (e.g., transapical versus transseptal); this outcome was not assessed in the CADTH rapid response report,[1] but during the development of our health technology assessment, stakeholders requested an analysis

Literature Screening

We did not conduct literature screening for the studies included in the CADTH rapid response report.[1] A single reviewer screened the two additional single-arm registry studies[18,19] that we identified.

Data Extraction

A single reviewer extracted relevant data on study characteristics and risk of bias as reported by CADTH,[1] as well relevant data from the two additional single-arm registry studies.

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, reporting of missing data, reporting of outcomes)

- Outcomes (e.g., outcomes measured, number of participants for each outcome, unit of measurement, time points at which the outcomes were assessed)

Statistical Analysis

The CADTH rapid response report[1] did not report a meta-analysis because of heterogeneity among the studies. We did not conduct further statistical analyses for this health technology assessment.

Critical Appraisal of Evidence

CADTH assessed risk of bias using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[21] and the Downs and Black[22] checklist; these assessments are described in this report. A single reviewer assessed risk of bias for the two additional single-arm registry studies[18,19] using the Downs and Black checklist (Appendix 1).

A single reviewer evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[23] A second reviewer undertook verification of all judgments (and support statements). The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The CADTH rapid response report[1] included 19 publications: one systematic review,[24] two observational retrospective comparative studies,[25,26] and 16 single-arm studies.[27-42] The two observational comparative studies compared TMViV with surgery.[25,26] Because our review focused specifically on people who were considered inoperable or high-risk for surgery, we excluded these studies from our analysis.

In addition to the studies from the CADTH rapid response report,[1] we included two single-arm registry studies[18,19] that also met our inclusion criteria. In total, our review included 19 publications: one systematic review[24] and 18 single-arm studies.[18,19,27-42]

Characteristics of Included Studies

The characteristics of the systematic review are shown in Table 1. The search dates reported for the systematic review[24] were from 2000 to March 30, 2018. This review had a broader scope than the CADTH rapid response report[1] and reviewed outcomes of TMViV procedures for degenerated mitral valve bioprosthetic valves and transcatheter mitral valves for failed annuloplasty rings. It included 101 studies,[24] of which 66 were relevant to the CADTH report,[1] because they reported outcomes related to TMViV for degenerated mitral valve bioprostheses. All studies included in the systematic review were single-arm. None of the 16 single-arm studies included in the CADTH rapid response report[1] nor the two single-arm studies[18,19] we identified were included in the systematic review.[24]

The characteristics of the 16 single-arm observational studies included in the CADTH rapid response report, along with the two additional single-arm registry studies[18,19] we identified, are shown in Table 2. Fourteen studies focused on TMViV and four studies focused on TTViV.

Table 1: Characteristics of Included Systematic Review

Author, year Country	Objective, study design	Participants	Intervention	Comparator	Outcomes
Hu et al, 2018[24] China	• To review the outcomes of TMViV for degenerated mitral bioprostheses and transcatheter mitral valve-in-ring for failed annuloplasty rings • 101 studies in total; 66 described TMViV for degenerated bioprostheses; designs of eligible studies not described (authors did not appear to exclude any study designs; all included studies were single-arm studies with no comparator group)	• 172 patients undergoing TMViV for degenerated mitral bioprostheses • Characteristics not available for every study • Mean age: 75 years (reported in 119 patients)	TMViV for degenerated mitral bioprostheses	None (NYHA class could be compared to baseline)	• In-hospital outcomes: success rate, mortality, bleeding, stroke, myocardial infarction, new arrythmia, acute kidney injury, NYHA class • 30-day and 6-month outcomes: death, stroke, myocardial infarction, thrombus, pseudoaneurysm, device failure, device migration

Abbreviations: NYHA, New York Heart Association; TMViV, transcatheter mitral valve-in-valve implantation.

Table 2: Characteristics of Included Observational Studies

Author, year Country	Objective Study design	Participants	Intervention[a]	Outcomes
Transcatheter mitral valve-in-valve implantation				
Guerrero et al, 2021[18,b] United States	Registry-based case series Retrospective	• 30 high-risk patients at 13 centres with symptomatic moderate to severe or severe mitral regurgitation or severe mitral stenosis due to failed surgical mitral bioprostheses • Median age: 77.5 years	TMViV using transseptal approach, Sapien 3	• Technical success • 30-day mortality • 1-year mortality • At 30 days and 1 year, freedom from: all stroke and TIA, myocardial infarction, major vascular complication, life-threatening bleeding
Simonato et al, 2021[19,b] Belgium, Brazil, Canada, Denmark, France, Israel, Italy, Germany, Netherlands, Portugal, Spain, United Kingdom, United States, Switzerland	Registry-based case series (Valve-in-Valve International Data [VIVID] registry) Retrospective	• 857 patients from 90 centres with degenerated mitral valve bioprostheses • Mean age: 71 years	TMViV using transapical or transseptal approach Patients treated most frequently with Sapien 3 (n = 607; 70.8%)	• Technical success • 30-day mortality • Vascular complications • Long-term survival
da Costa et al, 2020[27] Brazil	Case series Retrospective	• 50 patients at a single centre • Patients were selected for a transcatheter approach based on risk assessment (STS score ≥ 8 or EuroSCORE II ≥ 8.0, presence of comorbidities, number of previous surgeries, frailty, and general clinical condition) • Mean age: 65 years • Mean time since last valvular surgery: 12 years	TMViV through left anterolateral minithoracotomy for transapical access; valve was Braile Inovare	• Success rate • 30-day postoperative data: myocardial infarction, stroke, major vascular complications, major bleeding, acute renal failure, sepsis, mortality, NYHA class

Author, year Country	Objective Study design	Participants	Intervention[a]	Outcomes
Keenan et al, 2020[28] Australia	Case series Retrospective	• 7 patients at a single centre • Patients had structural deterioration of mitral bioprosthetic valves and were considered high-risk for redo valve surgery or young patients likely to require multiple reoperations • Mean age: 82 years • Median time since last TMViV: 11 years	Transseptal TMViV procedure using Edwards Sapien 3 valve	• Success rate • 30 days: mortality, stroke, bleeding, transfusion, major vascular complications, readmission, NYHA class
Okoh et al, 2020[29] United States	Case series Retrospective	• 15 patients with degenerative biological valve prosthesis considered high-risk for reoperative surgical mitral valve replacement • Mean age: 69 years	TMViV for failed bioprosthetic mitral valves (12 cases via transapical approach, 2 through median sternotomy, 1 via transseptal approach) Sapien XT in 10 patients, Sapien in 4 patients, Sapien S3 in 1 patient	• Procedural: success rate, acute kidney injury, myocardial infarction, disabling stroke, new-onset atrial fibrillation • 30 days: mortality, disabling stroke, rehospitalization, NYHA class • 1 year: mortality, NYHA class
Whisenant et al, 2020[30] United States	Registry-based case series Retrospective	• 1,529 patients at 295 centres • No explicit criteria outlined; authors noted that patients in study were older and had higher predicted operative risk than those undergoing reoperation in the same database registry • Mean age: 73 years	TMViV for degenerated bioprosthetic mitral valves using Edwards Sapien 3 valve (87% transseptal, 13% transapical)	• Primary outcomes: 1-year mortality, procedural technical success • Secondary outcomes: 30-day mortality, procedural complications, in-hospital cardiovascular mortality, in-hospital all-cause mortality, NYHA class, mitral valve performance

Author, year Country	Objective Study design	Participants	Intervention[a]	Outcomes
Yamashita et al, 2020[31] Japan	Case series Retrospective	• 4 patients with significant deterioration of implanted bioprosthetic valve, with stenosis, regurgitation, or both; heart failure with resistance to medications; high operative risk or contraindication to repeat replacement surgery (based on consensus of institutional heart team) at 1 institution • Patient characteristics not described statistically • Age range: 69 to 85 years	TMViV with Sapien XT valve via transapical approach	• NYHA class at 7 days compared to baseline • Median distance on 6-minute walk test at 7 days and 30 days compared to baseline • Adverse events within 30 days • Symptoms at last follow-up
Joseph et al, 2019[32] United States	Case series Retrospective	• 13 patients had significant mitral prosthetic dysfunction and comorbidities, precluding repeat valve surgery with sternotomy • Mean age: 75 years • Mean time since last valve replacement: 8 years • Mean previous sternotomies: 1.4	TMViV with Melody valve (transseptal puncture and apical rail)	• 30- day mortality, 1 year mortality, mortality to last follow-up (median 4.4 years) • NYHA class postimplant compared to preimplant, and reported mean NYHA class at 1, 3, and 5 years
Elmously et al, 2018[33] United States	Case series Retrospective	• 19 patients at one centre • Patients considered high-risk for redo surgical valve replacement • Mean age: 78 years	Transapical TMViV using Edwards Sapien valve	• Success rate at 30 days: mortality, stroke, myocardial infarction, blood transfusion • Last follow-up (mean 339 days): mortality, stroke, myocardial infarction, NYHA class

Author, year Country	Objective Study design	Participants	Intervention[a]	Outcomes
Eleid et al, 2017[34] Canada, France, United States	Case series Retrospective	• 60 patients with degenerated mitral bioprostheses • Patients had comorbid conditions precluding repeat sternotomy and valve replacement • Mean age: 75 years • 100% of patients had previous cardiac surgery	TMViV with Sapien, Sapien XT, Sapien 3 valves via transseptal approach	• Success rate • Procedural outcomes: conversion to open-heart surgery, myocardial infarction, stroke, emergency surgery, major bleeding, vascular complications • 30 days: mortality, NYHA class • 1 year: mortality, NYHA class
Gaia et al, 2017[35] Brazil	Case series Retrospective	• 12 patients with mitral prosthesis failure at 1 centre • Patients had dysfunctional bioprosthesis in mitral position, STS score > 8% or logistic EuroSCORE > 10, or clinical heart team judgment of high surgical risk • Mean age: 62 years	TMViV with Braile Inovare implanted through cardiac apex	• Postoperative mortality, 30-day and 1-year mortality, major cardiovascular events, 30-day and 1-year NYHA class, vascular complications, bleeding, cerebrovascular accident
D'Onofrio et al, 2016[36] Italy	Case series Retrospective	• 22 patients at 5 institutions • Patients had malfunctioning previously implanted bioprosthesis and were deemed inoperable or high-risk for conventional surgery for anatomic reasons, general clinical condition, or high predicted mortality rate • Mean age: 76 years	TMViV via transapical approach using Sapien valve	• 30 days: mortality, cardiovascular mortality, myocardial infarction, stroke • 1 year: NYHA class • 3 years: survival

Author, year Country	Objective Study design	Participants	Intervention[a]	Outcomes
Nachum et al, 2016[37] Israel	Case series Retrospective	• 9 patients with failed mitral bioprostheses at 1 centre • Patients considered high-risk for conventional redo mitral valve replacement due to advanced age, comorbidities, or frailty • Mean age: 82 years	Transapical TMViV procedure using Sapien valve	• Success rate, stroke, major bleeding • Follow-up (mean 13 months): mortality, NYHA class
Ye et al, 2015[38] Canada	Case series Retrospective	• 31 patients at a single centre • Patients had previous mitral valve replacement with bioprostheses and were deemed too high-risk for conventional redo valve replacement surgery • Mean age: 79 years	TMViV using Cribier Edwards equine, Sapien, and Sapien XT valves via transapical approach	• Success rate, intraoperative complications • Early clinical outcomes (30 days): life-threatening bleeding, major bleeding, disabling stroke, mortality, myocardial infarction, major vascular complications • 30 days: life-threatening bleeding, major bleeding, disabling stroke, mortality, myocardial infarction, major vascular complications • Long-term mortality • NYHA class at 2, 4, 5, and 6 years
Transcatheter tricuspid valve-in-valve implantation				
Viotto et al, 2019[39] Brazil	Case series Retrospective	• 7 patients with degenerated bioprosthesis in the tricuspid position at a single centre • All patients high or extreme risk for conventional approach • Mean age: 33 years • Median previous sternotomies: 3	TTViV using Braile Inovare, transapical access	• Success rate, periprocedural complications, NYHA class at follow-up

Author, year Country	Objective Study design	Participants	Intervention[a]	Outcomes
Landes et al, 2017[40] Israel	Case series Retrospective	• 7 patients between 2011 and 2016 at 5 centres • Standard reoperation overruled due to extremely high operative risk • Mean age: 63 years • Indication for valve intervention: stenosis (3 patients), regurgitation (1 patient), mixed (3 patients)	TTViV (4 Sapien XT, 3 Sapien 3) via transfemoral or transatrial approach	• Success rate, periprocedural complications, vascular complications • Follow-up (mean 8 months): NYHA class, mortality, stroke
McElhinney et al, 2016[41] Austria, Belgium, Canada, France, Germany, Italy, Portugal, Saudi Arabia, Switzerland, United States	Registry-based case series Retrospective	• 156 patients (no explicit criteria for inclusion) from 53 centres • Mean age: 40 years • Mean cardiac surgeries: 2 • Mean age of bioprosthesis: 7.4 years	TTViV; Melody (94 patients) or Sapien valves (58 patients; Sapien in 12 patients, Sapien XT in 41, Sapien 3 in 5); access via femoral vein, jugular vein, or right atrium	• NYHA class at 30 days and long-term follow-up (median of 13 months after procedure) • Included a formal statistical comparison of the proportion of patients in NYHA class I or II at 30 days and long-term follow-up compared to baseline
Ruparelia et al, 2016[42] Italy	Case series Retrospective	• 5 patients with tricuspid bioprosthesis failure at 1 centre • Patients had intractable symptoms despite optimal medical therapy and were considered high-risk for redo surgery • Age range: 49 to 75 years	TTViV using Sapien 3 via transfemoral venous route	• Success rate • 30 days: mortality, readmission, stroke, bleeding, myocardial infarction, NYHA class

Abbreviations: EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack; TMViV, transcatheter mitral valve-in-valve implantation; TTViV, transcatheter tricuspid valve-in-valve implantation.

[a]All included studies were single-arm studies.

[b]Additional study published in 2021 that was not included in the CADTH systematic review.[1]

Risk of Bias in the Included Studies

SYSTEMATIC REVIEW

CADTH[1] assessed the systematic review[24] using AMSTAR 2. They did not calculate summary scores; instead, they described the strengths and limitations of the systematic review narratively. Overall, CADTH noted that the systematic review had several methodological concerns:

- Two databases were examined for the literature search, but the authors did not describe whether they also searched reference lists, grey literature, or trial registries
- Details were lacking related to the population, intervention, comparators, and outcomes of the systematic review
- No details or risk of bias assessment were provided for the included studies
- It was unclear whether the method of combining NYHA class data was appropriate (number of patients at NYHA class III or higher before and after surgery)
- Sources of heterogeneity between studies were not described
- All studies were single-arm studies, and the total number of patients included was 172; however, some outcomes were analyzed with a low number of patients (e.g., the before/after comparison of NYHA class included 57 patients before surgery and 39 patients after)

OBSERVATIONAL STUDIES

CADTH[1] assessed the risk of bias of the observational studies using the Downs and Black[22] checklist. They did not calculate summary scores; instead, they described the strengths and limitations of the studies narratively.[1] Studies were generally well-reported and clearly described the aims, outcomes, and findings.[24] The risk of bias or limitations reported by CADTH[1] for the single-arm observational studies were as follows:

- The lack of comparator groups made it impossible to draw conclusions about the relative efficacy and safety of TMViV or TTViV procedures compared to medical management.[1] Studies did report NYHA class at baseline and follow-up, permitting the comparison of functional status before and after the procedure; two studies, Joseph et al[32] and McElhinney et al[41]) reported a formal statistical comparison of NYHA before and after the procedure
- The studies had small sample sizes (11 of 12 TMViV studies had sample sizes of 60 or fewer, and three of four TTViV studies had sample sizes of seven or less). The studies were conducted at one centre or a few centres, making it unclear whether the included patients were representative of typical patients undergoing such procedures[1]
- One study[30] included all patients (N = 1,529) who underwent TMViV in a voluntary registry at 295 sites from 2015 to 2019, and may offer greater generalizability. Eleven of the 16 single-arm studies reported on consecutive patients at their centre; this suggests that the patients may have been representative of all patients who received TMViV or TTViV[1]

Our assessment of risk of bias for the two additional single-arm studies using the Downs and Black checklist is reported in Appendix 1, Table A1. Similar to CADTH,[1] we did not calculate summary scores, describing the results narratively instead. The risk of bias and limitations of the two additional

observational studies[18,19] were similar to those reported by CADTH[1] for the previously mentioned observational studies:

- The studies lacked a comparator group
- The studies were retrospective registry studies with sample sizes of N = 30[18] and N = 867[19]
- Both studies were missing data because of loss to follow-up
- Simonato et al[19] noted that their included procedures were spread over 90 international centres and a long period of time (14 years); Guerrero et al[18] stated that their included procedures occurred between July 2016 and October 2017 at 13 centres in the United States

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MORTALITY

Results from the systematic review[24] and the single-arm studies of TMViV for degenerated mitral bioprosthetic valves are shown in Table 3. Overall, ranges for in-hospital, 30-day and 1-year mortality were 0% to 5%, 0% to 15%, and 0% to 27%, respectively.

Table 3: Summary of TMViV Results, Mortality

Study	Deaths/patients, n/N (%)
In-hospital	
Guerrero et al, 2021[18]	1/30 (3.3); procedural
Simonato et al, 2021[19]	18/857 (2.1); procedural
da Costa et al, 2020[27]	1/50 (2); intraoperative
Okoh et al, 2020[29]	0/15 (0)
Whisenant et al, 2020[30]	61/1,529 (4)
Joseph et al, 2019[32]	0/13 (0)
Hu et al, 2018[24]	All-cause: 9/172 (5.2) Cardiovascular: 5/172 (2.9)
Eleid et al, 2017[34]	2/60 (5); periprocedural
Gaia et al, 2017[35]	0/12 (0); operative
Nachum et al, 2016[37]	0/9 (0); procedural
30-day follow-up	
Guerrero et al, 2021[18]	1/30 (3.3)
Simonato et al, 2021[19]	56/857 (6.5)
da Costa et al, 2020[27]	6/50 (12)
Keenan et al, 2020[28]	1/7 (14)
Okoh et al, 2020[29]	0/15 (0)

Study	Deaths/patients, n/N (%)
Whisenant et al, 2020[30]	78 (5.4)[a]
Joseph et al, 2019[32]	2/13 (15.4)
Elmously et al, 2018[33]	0/9 (0)
Hu et al, 2018[24]	11/147 (7.5)
Eleid et al, 2017[34]	3/60 (5)
D'Onofrio et al, 2016[36]	2/22 (9)
Ye et al, 2015[38]	0/31 (0)
6-month follow-up	
Hu et al, 2018[24]	16/85 (18.8)
1-year follow-up	
Guerrero et al, 2021[18]	1/30 (3.3)
Simonato et al, 2021[19]	13.8% (survival reported as 86.2%)[a]
Okoh et al, 2020[29]	4/15 (27)
Whisenant et al, 2020[30]	16.7%[a]
Joseph et al, 2019[32]	25%[a]
Elmously et al, 2018[33] (mean 339 days)	1/19 (5)
Eleid et al, 2017[34]	14% (survival reported as 86.0%)[a]
Nachum et al, 2016[37] (mean 13 months)	0/9 (0)
Longer-term follow-up	
Joseph et al, 2019[32]	6/13 (46); median follow-up 4.4 years
Gaia et al, 2017[35]	1/12 (8); median follow-up 612 days
D'Onofrio et al, 2016[36]	9% (survival reported as 91%)[a]; 3 years
Simonato et al, 2014[19]	37.5% (survival reported as 62.5%)[a]; 4 years

Abbreviation: TMViV, transcatheter mitral valve-in-valve implantation.
[a]Calculated from Kaplan–Meier curve; not possible to give proportion.

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A2).

STROKE

Results from the systematic review[24] and single-arm studies of TMViV for degenerated mitral bioprosthetic valves are shown in Table 4. Overall, rates of stroke occurring in hospital or at 30-day or 6-month follow-up were 0% to 8.3%, 0% to 3.3%, and 1.4% to 5.4%, respectively. Rates of stroke occurring at 1-year follow-up ranged from 3.3% to 6.7%.

Table 4: Summary of TMViV Results, Stroke

Study	Strokes/patients, n/N (%)
In-hospital	
Simonato et al, 2021[19]	12/857 (1.4); procedural
Whisenant et al, 2020[30]	10/1,529 (0.7); procedural
Hu et al, 2018[24]	3/172 (1.7)
Eleid et al, 2017[34]	0/60 (0); after the procedure
Gaia et al, 2017[35]	1/12 (8.3); procedural
Nachum et al, 2016[37]	0/9 (0); early stroke
30-day follow-up	
Guerrero et al, 2021[18]	1/30 (3.3)
da Costa et al, 2020[27]	1/50 (2)
Keenan et al, 2020[28]	0/7 (0)
Okoh et al, 2020[29]	0/15 (0)
Whisenant et al, 2020[30]	16 (1.1)[a]
Elmously et al, 2018[33]	0/19 (0)
Hu et al, 2018[24]	3/95 (3.2)
D'Onofrio et al, 2016[36]	0/22 (0)
Ye et al, 2015[38]	1/31 (1.4)
6-month follow-up	
Hu et al, 2018[24]	3/56 (5.4)
Ye et al, 2015[38]	1/31 (1.4); > 30 days
1-year follow-up	
Guerrero et al, 2021[18]	2/30 (6.7)
Whisenant et al, 2020[30]	32 (3.3)[a]

Abbreviation: TMViV, transcatheter mitral valve-in-valve implantation.
[a]Calculated from Kaplan–Meier curve; not possible to give proportion.

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A2).

MYOCARDIAL INFARCTION

Results from the systematic review[24] and the additional single-arm studies of TMViV for degenerated mitral bioprosthetic valves are shown in Table 5. Overall, rates of myocardial infarction in-hospital or at 30-day follow-up were 0 to 0.3% and 0 to 4.5%, respectively. Three studies reported that no patients experienced a myocardial infarction at 6-month follow-up after TMViV.[18,24,38]

Table 5: Summary of TMViV Results, Myocardial Infarction

Study	Myocardial infarctions/patients, n/N (%)
In-hospital	
Guerrero et al, 2021[18]	0/30 (0); procedural
Whisenant et al, 2020[30]	5/1,529 (0.3); periprocedural
Hu et al, 2018[24]	0/172 (0)
Eleid et al, 2017[34]	0/60 (0); after the procedure
30-day follow-up	
Guerrero et al, 2021[18]	0/30 (0)
da Costa et al, 2020[27]	2/50 (4)
Okoh et al, 2020[29]	0/15 (0)
Elmously et al, 2018[33]	0/19 (0)
Hu et al, 2018[24]	0/95 (0)
D'Onofrio et al, 2016[36]	1/22 (4.5)
Ye et al, 2015[38]	0/31 (0)
6-month follow-up	
Guerrero et al, 2021[18]	0/30 (0)
Hu et al, 2018[24]	0/53 (0)
Ye et al, 2015[38]	0/31 (0); > 30 days

Abbreviation: TMViV, transcatheter mitral valve-in-valve implantation.

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A2).

NYHA FUNCTIONAL CLASS

Results from the systematic review[24] and the single-arm studies of TMViV for degenerated mitral bioprosthetic valves are shown in Table 6. Overall, patients experienced functional improvement related to heart failure symptoms (reported as a lower NYHA class) after undergoing TMViV at various follow-up intervals compared to before TMViV. Hu et al[24] reported significantly fewer patients with NYHA class III

or IV after TMViV during in-hospital follow-up compared to before TMViV ($P < .001$). At 30-day follow-up, Joseph et al[32] reported significantly fewer patients with NYHA class III or IV after TMViV ($P < .05$).

Table 6: Summary of TMViV Results, NYHA Functional Class

Study	NYHA class
In-hospital	
Hu et al, 2018[24]	NYHA ≥ III, n/N (%) Preimplant, 57/57 (100%) Postimplant, 1/39 (2.6%) *P* < 0.001
30-day follow-up	
Guerrero et al, 2021[18]	NYHA class, n/N (%) Baseline, 0 (0%) class I, 6/30 (20%) class II, 20/30 (66.7%) class III, 4/30 (13.3%) class IV 30 days, 14/29 (48.3%) class I, 10/29 (34.5%) class II, 5/29 (17.2%) class III, 0/29 (0%) class IV *P* value NR
da Costa et al, 2020[27]	NYHA ≤ II Baseline, 20% 30 days, 95.4% *P* value NR
Keenan et al, 2020[28]	NYHA I, n/N (%) Baseline, 0/7 (0%) 30 days, 6/6 (100%) *P* value NR
Okoh et al, 2020[29]	NYHA I or II, n/N (%) Baseline, 3/15 (20%) 30 days, 15/15 (100%) *P* value NR
Whisenant et al, 2020[30]	NYHA I or II, n/N (%) Baseline, 195/1,510 (13%) 30 days, 854/994 (86%) *P* value NR
Yamashita et al, 2020[31]	Median NYHA class (range) Baseline, 2 (1–3) 30 days, 1 (1–2) *P* value NR
Joseph et al, 2019[32]	NYHA ≥ III, n/N (%) Preimplant, 13/13 (100%) Postimplant, 2/11 (18%) *P* < .05
Gaia et al, 2017[35]	NYHA class, n/N (%): Baseline, 12 (100%) class IV 30 days, 7 (58%) class I, 4 (33%) class II, 1 (8%) class III *P* value NR
1-year follow-up	
Guerrero et al, 2021[18]	NYHA class, n/N (%): Baseline, 0 (0%) class I, 6/30 (20%) class II, 20/30 (66.7%) class III, 4/30 (13.3%) class IV

Study	NYHA class
	1 year, 10/28 (35.7%) class I, 15/28 (53.6%) class II, 3/28 (10.7%) class III, 0/28 (0%) class IV *P* value NR
Whisenant et al, 2020[30]	NYHA class I or II, n/N (%) Baseline, 195/1,510 (13%) 1 year 318/352 (90%) *P* value NR
Joseph et al, 2019[32]	NYHA class, mean ± SD Preimplant, 3.5 ± 0.5 1 year, 1.9 ± 0.8 *P* value NR
Eleid et al, 2017[34]	NYHA class, n/N (%) Baseline, 27 (45%) class III, 33 (55%) class IV 1 year, 18 (68%) class I, 8 (28%) class II, 1 (2%) class III *P* value NR
Gaia et al, 2017[35]	NYHA class, n/N (%) Baseline, 12 (100%) class IV 1 year, 6 (67%) class I, 3 (33%) class II *P* value NR
D'Onofrio et al, 2016[36]	NYHA class, %[a] Baseline, ~65% class III, ~35% class IV 1 year, ~65% class I, ~30% class II, ~5% class III *P* value NR
Longer-term follow-up	
Joseph et al, 2019[32]	NYHA class, mean ± SD Preimplant, 3.5 ± 0.5 3 years, 1.8 ± 1.0 5 years, 2.0 ± 0.8 *P* value NR
Elmously et al, 2018[33]	NYHA class I or II, n/N (%) Baseline, 0/19 (0%) Mean 339 days follow-up, 17/19 (89.5%) *P* value NR
Nachum et al, 2016[37]	NYHA class I or II, n/N (%) Baseline 0/9 (0%) Mean 13 months follow-up 9/9 (100%) *P* value NR
Ye et al, 2015[38]	NYHA class I or II, n/N (%) Baseline, 0% 2 years, 100% *P* value NR

Abbreviations: NYHA, New York Heart Association; NR, not reported; SD, standard deviation; Abbreviation: TMViV, transcatheter mitral valve-in-valve implantation.

[a]Percent of patients estimated from figure; numerical data not provided.

We rated the certainty of the evidence as low, downgrading for risk of bias and upgrading for the large effect size reported in studies that conducted a statistical comparison (Appendix 1, Table A2).

COMPLICATIONS

Results from the systematic review[24] and the additional single-arm studies of TMViV for degenerated mitral bioprostheses are shown in Table 7. Overall, rates of bleeding complications in hospital and at 30-day or 6-month follow-up were 7% to 11%, 4% to 14% and 0% (1 study), respectively. Rates of kidney complications in hospital or at 30-day follow-up were 0% to 7.7% and 0% to 30%, respectively.

Table 7: Summary of TMViV Results, Complications

Study	Complications/patients, n/N (%)
In-hospital, bleeding	
Simonato et al, 2021[19]	Major bleeding: 75/857 (8.8)
Hu et al, 2018[24]	15/172 (8.7)
Eleid et al, 2017[34]	Procedural major bleeding: 4/60 (7.0)
Nachum et al, 2016[37]	Early major bleeding: 1/9 (11.0)
In-hospital, cardiac complications	
Elmously et al, 2018[33]	Postoperative cardiac arrest with complete cardiovascular/neurological recovery: 2/19 (10.5)
In-hospital, major vascular complications	
Guerrero et al, 2021[18]	0/30 (0)
Simonato et al, 2021[19]	27/857 (3.2)
Whisenant et al, 2020[30]	21/1,529 (1.4)
Gaia et al, 2017[35]	1/12 (8.3)
In-hospital, kidney complications	
Simonato et al, 2021[19]	Acute kidney injury: 75/857 (8.8)
Joseph et al, 2019[32]	Acute kidney injury: 1/13 (7.7)
Hu et al, 2018[24]	Acute kidney injury: 7/172 (4.1)
Gaia et al, 2017[35]	Procedural acute kidney injury: 0/12 (0)
30-day follow-up, bleeding	
Guerrero et al, 2021[18]	Transfusion: 3/30 (10)
da Costa et al, 2020[27]	Major bleeding 2/50 (4.0)
Keenan et al, 2020[28]	Transfusion within 30 days: 3/7 (42.8) Bleeding: 1/7 (14.2)
Ye et al, 2015[38]	Major bleeding: 6/31 (19.4)
30-day follow-up, thrombus	
Hu et al, 2018[24]	3/95 (3.2)
30-day follow-up, major vascular complications	
Guerrero et al, 2021[18]	1/30 (3.3)
da Costa et al, 2020[27]	3/50 (6.0)
Keenan et al, 2020[28]	0/7 (0)
30-day follow-up, sepsis	
da Costa et al, 2020[27]	14/50 (28.0)

Study	Complications/patients, n/N (%)
30-day follow-up, readmission	
Keenan et al, 2020[28]	1/7 (14.0)
Okoh et al, 2020[29]	0/15 (0)
Elmously et al, 2018[33]	0/19 (0)
30-day follow-up, kidney complications	
Guerrero et al, 2021[18]	Acute kidney injury requiring hemodialysis: 0/30 (0)
da Costa et al, 2020[27]	Acute renal failure: 15/50 (30.0)
Keenan et al, 2020[28]	Acute kidney failure: 1/7 (14.0)
Okoh et al, 2020[29]	Acute kidney injury: 1/15 (6.7)
Whisenant et al, 2020[30]	New dialysis requirement: 24 (1.7)[a]
D'Onofrio et al, 2016[36]	Acute kidney injury: 0/12 (0)
Ye et al, 2015[38]	Acute renal failure requiring hemodialysis: 1/31 (3.2)
30-day follow-up, device-related	
Guerrero et al, 2021[18]	Device embolization or migration: 0/30 (0)
Hu et al, 2018[24]	Device migration: 5/95 (5.3)
6-month follow-up, bleeding	
Ye et al, 2015[38]	Major bleeding: 0/31 (0)
6-month follow-up, thrombus	
Hu et al, 2018[24]	5/60 (8.3)
6-month follow-up, device-related	
Hu et al, 2018[24]	Device migration: 7/60 (11.7) Device failure: 3/54 (5.6)
1-year follow-up, bleeding	
Guerrero et al, 2021[18]	Transfusion: 6/30 (20)
1-year follow-up, kidney complications	
Guerrero et al, 2021[18]	Acute kidney injury requiring hemodialysis: 0/30 (0)
1-year follow-up, major vascular complications	
Guerrero et al, 2021[18]	1/30 (3.3)
1-year follow-up, device-related	
Guerrero et al, 2021[18]	Device embolization or migration: 0/30 (0)

Abbreviation: TMViV, transcatheter mitral valve-in-valve implantation.

[a]Calculated from Kaplan–Meier curve; not possible to give proportion.

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A2).

HOSPITAL OR INTENSIVE CARE UNIT STAY

The case series by Whisenant et al[30] reported that the median (interquartile range) length of hospital stay for patients who underwent TMViV was 3.0 days (2.0 to 6.0 days).

We rated the certainty of the evidence as very low, downgrading for risk of bias (Appendix 1, Table A2).

SUBANALYSIS OF TRANSCATHETER ACCESS ROUTES

The systematic review by Hu et al[24] reported that different access routes (transapical or transseptal) did not significantly affect patients' clinical outcomes or overall survival (Table 8).

Table 8: Subanalysis, Transapical Versus Transseptal Access (Hu et al[24])

Outcome	Transapical access, n/N (%)	Transseptal access, n/N (%)	*P* value
Death	3/94 (3.2)	4/61 (6.6)	.55
Stroke	2/94 (2.1)	1/61 (1.6)	> .99
Myocardial infarction	0/94 (0.0)	0/61 (0.0)	—
NYHA class ≤ II at last follow-up	46/49 (93.9)	12/12 (100.0)	> .99
Acute kidney injury	8/94 (8.5)	2/61 (3.3)	.34
Bleeding	8/94 (8.5)	5/61 (8.2)	.95
Thrombus	1/94 (1.1)	0/61 (0.0)	> .99
Survival[a]	NR	NR	.45

Abbreviations: NYHA, New York Heart Association; NR, not reported.

[a]Kaplan–Meier overall survival.

Whisenant et al[30] reported a significantly shorter hospital length of stay for patients who underwent transseptal versus transapical TMViV access ($P < .001$; Table 9). At in-hospital follow-up, there were significantly more cardiovascular deaths in patients who underwent transapical versus transseptal access ($P = .03$). At 30-day follow-up, transseptal access was associated with significantly lower cardiovascular death rates than transapical access ($P = .01$). At 1-year follow-up, transseptal access had significantly lower all-cause mortality rates than transapical access ($P = .03$).

Table 9: Subanalysis, Transapical Versus Transseptal Access (Whisenant et al[30])

Outcome	Transapical access, n/N (%)	Transseptal access, n/N (%)	*P* value
In-hospital			
All-cause mortality	13/203 (6.4)	48/1,326 (3.6)	.06
Cardiovascular death	9/203 (4.4)	24/1,326 (1.8)	.03
Stroke	1/203 (0.5)	9/1,326 (0.7)	> .99
Myocardial infarction	1/203 (0.5)	4/1,326 (0.3)	.51
Major vascular complications	5/203 (2.5)	16/1,326 (1.2)	.18
Length of stay, median (IQR)	6 (3–9)	2 (1–5)	< .001
30-day follow-up			
Death	16 (8.1)	62 (5.0)	.07
Cardiovascular death	10 (5.1)	26 (2.1)	.01
Stroke	16 (1.1)	14 (1.1)	.91
NYHA class I	58/131 (44.3)	385/863 (44.6)	.94
NYHA class II	55/131 (42.0)	356/863 (41.3)	.87
NYHA class III	13/131 (9.9)	106/863 (12.3)	.44
NYHA class IV	5/131 (3.8)	16/863 (1.9)	.18
1-year follow-up			
All-cause mortality	37 (21.7)	138 (15.8)	.03
Cardiovascular death	11 (5.7)	36 (3.7)	.07
Stroke	5 (3.5)	27 (3.3)	.95
NYHA class I	30/62 (48.4)	143/290 (49.3)	.89
NYHA class II	26/62 (41.9)	119/290 (41.0)	90
NYHA class III	5/62 (8.1)	23/290 (7.9)	> .99
NYHA class IV	1/62 (1.6)	5/290 (1.7)	> .99

Abbreviations: IQR, interquartile range; NYHA, New York Heart Association.

In the Valve-in-Valve International Data (VIVID) registry study, Simonato et al[19] reported no significant survival difference at 4 years between patients who underwent a procedure with transseptal access (n = 296) and those who underwent procedures that used other access routes (58.6% versus 59.9%; *P* = .59). The access route subanalysis for that study included data for patients who underwent both TMViV (n = 857) and mitral valve-in-ring (n = 222) procedures (i.e., data for the TMViV group only were not reported).

Transcatheter Tricuspid Valve-in-Valve Implantation

MORTALITY

Results for four single-arm studies[39-42] of TTViV for degenerated tricuspid bioprostheses are shown in Table 10. Overall, 30-day and 1-year (or longer) mortality were 0% to 3% and 0% to 14%, respectively.

Table 10: Summary of TTViV Results, Mortality

Study	Deaths/patients, n/N (%)
30-day follow-up	
McElhinney et al, 2016[41]	5/152 (3)
Ruparelia et al, 2016[42]	0/5 (0)
1-year follow-up	
Landes et al, 2017[40]	1/7 (14); mean 8 months
McElhinney et al, 2016[41]	17/152 (11); median 13 months
Longer-term follow-up	
Viotto et al, 2019[39]	0/7 (0); mean 1.2 years

Abbreviation: TTViV, transcatheter tricuspid valve-in-valve implantation.

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A3).

STROKE

Results for two single-arm studies[40,42] of TTViV for degenerated tricuspid bioprostheses are shown in Table 11. Overall, the 30-day and 6-month occurrences of stroke were 0% and 14%, respectively.

Table 11: Summary of TTViV Results, Stroke

Study	Strokes/patients, n/N (%)
30-day follow-up	
Ruparelia et al, 2016[42]	0/5 (0)
6-month follow-up	
Landes et al, 2017[40]	1/7 (14); mean 8 months

Abbreviation: TTViV, transcatheter tricuspid valve-in-valve implantation.

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A3).

MYOCARDIAL INFARCTION

One single-arm study of TTViV for degenerated tricuspid bioprostheses reported that the occurrence of myocardial infarction at 30-day follow-up was 0% (0 of 5 patients).[42]

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A3).

NYHA FUNCTIONAL CLASS

Results for four single-arm studies[39-42] of TTViV for degenerated tricuspid bioprostheses are shown in Table 12. Overall, patients experienced functional improvement related to heart failure symptoms (reported as a lower NYHA class) at various follow-up intervals after TTViV compared to before TTViV. McElhinney et al[41] reported a significant decrease in the number of patients who obtained NYHA class III or IV at a median 13-month follow-up compared to baseline ($P < .00001$).

Table 12: Summary of TTViV Results, NYHA Functional Class

Study	NYHA class
30-day follow-up	
Ruparelia et al, 2016[42]	NYHA class, n Baseline, 4 class III, 1 class IV 30 days, 4 class I, 1 class II *P* value NR
1-year follow-up	
Landes et al, 2017[40]	NYHA class, n (%) Baseline, 1 (14%) class II, 2 (29%) class III, 4 (57%) class IV Mean 8 months, 3 (50%) class I, 3 (50%) class II *P* value NR
McElhinney et al, 2016[41]	NYHA class III or IV, % Baseline 71% Median 13 months, 15% *P* < .00001
Unspecified follow-up	
Viotto et al, 2019[39]	NYHA class, n Baseline, 4 class II, 1 class III, 2 class IV Follow-up 6 class I, 1 class II *P* value NR

Abbreviations: NYHA, New York Heart Association; NR, not reported; TTViV, transcatheter tricuspid valve-in-valve implantation.

We rated the certainty of the evidence as low, downgrading for risk of bias and upgrading for the large effect size reported in the study that conducted a statistical comparison (Appendix 1, Table A3).

COMPLICATIONS

Results for three single-arm studies of TTViV for degenerated tricuspid bioprostheses are shown in Table 13. Overall, in-hospital kidney or major vascular complications were observed in 14% and 29% of patients, respectively.[39,40] At 30-day follow-up, no bleeding or readmission was reported, but 20% of patients experienced acute kidney injury.[42]

Table 13: Summary of TTViV Results, Complications

Study	Complications/patients, n/N (%)
In-hospital, major vascular complications	
Landes et al, 2017[40]	Periprocedural: 1/7 (14)
In-hospital, kidney complications	
Viotto et al, 2019[39]	Postoperative acute kidney injury with no need for dialysis: 2/7 (29)
30-day follow-up, bleeding	
Ruparelia et al, 2016[42]	0/5 (0)
30-day follow-up, readmission	
Ruparelia et al, 2016[42]	0/5 (0)
30-day follow-up, kidney complications	
Ruparelia et al, 2016[42]	Acute kidney injury at 30 days: 1/5 (20)

Abbreviation: TTViV, transcatheter tricuspid valve-in-valve implantation.

We rated the certainty of the evidence as very low, downgrading for risk of bias and imprecision (Appendix 1, Table A3).

HOSPITAL OR INTENSIVE CARE UNIT STAY

None of the studies reported this outcome.

Discussion

Transcatheter Mitral Valve-in-Valve Implantation

Overall, in-hospital, 30-day and 1-year mortality rates in patients who underwent TMViV were 0% to 5%, 0% to 15%, and 14% to 27%, respectively. All TMViV studies but two[19,30] had sample sizes of 60 patients or fewer (range, 5 to 60 patients). The two largest and most recent studies included 1,529 and 857 patients,[19,30] and using Kaplan–Meier curves, 1-year mortality in those studies was 16.7%[30] and 13.8%.[19] Whisenant et al[30] did not report results from a longer follow-up, but Simonato et al[19] reported a 4-year mortality of 37.5%. Both of these studies used data from registries that had limitations, including retrospective design, lack of a control group, missing data because of patients lost to follow-up, data collection over long time periods (14 years for Simonato et al[19] and 4 years for Whisenant et al[30]), and variable transcatheter access routes (e.g., transapical or transseptal). Transapical access has been used less commonly over time because of maturation of the technique and technology.[19,30]

It is interesting to compare the mortality rates associated with TMViV in our health technology assessment to those of patients with mitral regurgitation who received medical or drug therapy alone. Ling et al[6] studied 229 patients who underwent medical treatment for mitral regurgitation because of flail leaflet and observed that 5- and 10-year all-cause mortality rates (mean ± standard error) were 28 ± 4% and 43 ± 7%, respectively. Unlike the population in the present health technology assessment, the patients in the study by Ling et al[6] did not have an existing prosthetic valve implant, and a majority (110/229) were in NYHA class I.

In the present health technology assessment, NYHA functional class was the only outcome with statistical testing to compare results before and after TMViV. Most patients in the TMViV studies were in NYHA class III and IV before TMViV. Overall, studies consistently showed that compared to before TMViV, patients experienced functional improvement related to heart failure symptoms (reported as a lower NYHA class) at various follow-up intervals. The included systematic review by Hu et al[24] reported significantly fewer patients in NYHA class III or IV during in-hospital follow-up after TMViV compared to before TMViV. At 30-day follow-up, Joseph et al[32] reported significantly fewer patients in NYHA class III or IV after TMViV.

In the study of mitral regurgitation treated with medical therapy described above, Ling et al[6] noted that of the 66 patients in NYHA class III or IV at baseline, 49 (74%) eventually had surgery. The other 17 patients continued to be treated medically because of high estimated risk associated with surgery (n = 6) or functional improvement with treatment (n = 11).[6] However, despite the functional improvement that many experienced, the outcome for these medically treated patients was poor (yearly mortality 34%) and worse than the outcome for patients in NYHA class I or II (hazard ratio, 8.23; 95% confidence interval, 4.22 to 16.05; $P < 0.001$).[6] This finding indicated that patients who are severely symptomatic (i.e., NYHA class III or IV), similar to the patient population in this health technology assessment (inoperable or high-risk for surgery), may have very poor outcomes while on medical or drug therapy.

The largest included study, by Whisenant et al,[30] assessed 1,529 patients (1,326 undergoing a transseptal procedure [86.7%] and 203 undergoing a transapical procedure [13.3%]). In subanalyses of transapical versus transseptal access during TMViV, the authors reported that transseptal access was associated with a significantly shorter hospital length of stay, significantly fewer cardiovascular deaths at 30 days, and significantly lower all-cause mortality at 1 year compared to transapical access. Furthermore, during in-hospital follow-up, there were significantly more cardiovascular deaths among patients who underwent a transapical compared to a transseptal procedure. In another registry study by Simonato et al (N = 857),[19] transapical access was used in the majority of cases. Although transapical access had been associated with worse outcomes in aortic procedures,[19] the authors did not identify a survival difference between access routes.[19] They speculated that even though procedural invasiveness is reduced with transseptal access, survival differences may be more related to patient characteristics than to procedural factors.

Strengths and limitations of the TMViV studies in this health technology assessment included the following:

- Two large registry studies (Simonato et al[19] [N = 857] and Whisenant et al[30] [N = 1,529]) included all patients who underwent TMViV in voluntary registries at multiple sites and may offer greater generalizability

- Whisenant et al[30] reported a longitudinal analysis that demonstrated lower 30-day mortality with each successive year since 2015. The authors stated that a major inflection point roughly coincided with a transition from transapical to transseptal procedures, followed by continually improving outcomes after 2015, consistent with increased TMViV experience and increasing conversion to transseptal access[30]
- A lack of a comparison group made it impossible to draw conclusions about the relative efficacy and safety of TMViV compared to medical management (standard care).[1] Although all studies reported NYHA functional class at baseline and follow-up, allowing the comparison of functional status before and after the procedure, only two studies[24,32] made a formal statistical comparison of NYHA functional class before and after TMViV
- Sample sizes were small (12 of 14 TMViV studies had sample sizes of 60 or fewer). The studies were conducted at one or a few centres, making it unclear whether the included patients were representative of typical patients who undergo such procedures[1]

Transcatheter Tricuspid Valve-in-Valve Implantation

Four studies, with sample sizes ranging from five patients to a registry of 152 patients, reported outcomes for TTViV. Overall, 30-day and 1-year (or longer) mortality were 0% to 3% and 0% to 14%, respectively. The registry study with the largest sample size (N = 152) reported 22 deaths over a median follow-up period of 13.3 months (range 0.1 to 61 months).[41] Five patients died within 30 days of implantation, all of whom were in NYHA class III or IV at baseline, including two who underwent TTViV as compassionate cases.[41] During follow-up, 17 additional patients died, 10 within a year of TTViV. Including early mortality, causes of death were related to the procedure in one patient (a 71-year-old who also underwent exchange of a right subclavian venous dialysis catheter during the TTViV catheterization, developed a localized posterior hemopericardium of unknown cause, and died of tamponade the following day); cardiovascular but unrelated to the procedure in 14 patients; and not cardiovascular in seven patients.[41] All 22 patients who died were in NYHA class III or IV before TTViV, and nine had been hospitalized and were acutely ill before the procedure.[41]

In terms of the natural history of tricuspid regurgitation on mortality, Nath et al[7] studied 601 patients (11.5%) with no tricuspid regurgitation, 3,805 patients (68.8%) with mild tricuspid regurgitation, 620 patients (11.8%) with moderate tricuspid regurgitation, and 199 patients (3.8%) with severe tricuspid regurgitation. They reported that the 1-year mortality rates for patients with moderate or severe tricuspid regurgitation were 36% and 21%, respectively.[7] They also noted that patients with moderate or severe tricuspid regurgitation were generally older and had worse ventricular function than those with no or mild tricuspid regurgitation. Five-year and 10-year survival rates for moderate or severe tricuspid regurgitation are 51.7% and 30.5%, respectively.[8]

Overall, all four studies indicated that patients experienced functional improvement related to heart failure symptoms after undergoing TTViV at various follow-up intervals compared to before the procedure. McElhinney et al[41] reported a significant decrease in the number of patients in NYHA class III or IV at a median 13 months of follow-up compared to baseline.

Strengths and limitations of the TTViV studies in this health technology assessment included the following:

- A lack of a comparison group made it impossible to draw conclusions about the relative efficacy and safety of TTViV compared to medical management (standard care).[1] Although all studies reported NYHA functional class at baseline and follow-up, allowing the comparison of functional status before and after the procedure, only one study[41] made a formal statistical comparison of NYHA functional class before and after TTViV
- Sample sizes were small (three of four TTViV studies had sample sizes of seven or less). The studies were conducted at one or a few centres, making it unclear whether the included patients were representative of typical patients who undergo such procedures[1]
- The study by McElhinney et al[41] included all patients (N = 156) from 53 centres who underwent TTViV in a voluntary multisite registry and may offer greater generalizability. Nevertheless, the authors stated that although they solicited participation in the registry widely, invitations were not universally accepted and they may not have captured all cases of TTViV[41]

Strengths and Limitations

Strengths of this health technology assessment included the following:

- We leveraged a recent CADTH rapid response report[1] and modified the inclusion criteria to appropriately focus on people who are considered inoperable or high-risk for surgery
- We supplemented the results of the CADTH rapid response report by including two recent studies,[18,19] one of which had a large sample size (N = 857) and reported cases from the Valve-in-Valve International Data (VIVID) registry[19]
- The three large registry studies[19,30,41] we included may offer greater generalizability than the small, single-centre studies

A limitation was that we did not conduct a literature search because the CADTH rapid response report[1] was very recent (October 2020) and we considered their literature search to be appropriate and comprehensive. Our expert consultants were in agreement with this approach.

Conclusions

For people with degenerated mitral or tricuspid bioprosthetic valves and who are considered inoperable or high-risk for surgery, TMViV or TTViV:

- May reduce mortality, but the evidence is very uncertain
- May reduce stroke, myocardial infarction, or other complications, but the evidence is very uncertain
- May improve NYHA functional class

Economic Evidence

A rapid response report from the Canadian Agency for Drugs and Technologies in Health (CADTH) on transcatheter valve-in-valve implantation for degenerated mitral or tricuspid bioprostheses was published in October 2020.[1] That review evaluated the clinical effectiveness and cost-effectiveness of transcatheter valve-in-valve implantation for degenerated mitral or tricuspid bioprostheses; comparators were a second open-heart valve replacement surgery, medical management, or before-and-after comparisons of the intervention. The literature search for the CADTH report[1] included studies published between January 1, 2015, and July 29, 2020, in key databases (e.g., Medline, Embase, the Cochrane Library, etc.) and found no relevant cost-effectiveness studies.

We also conducted a hand search of the grey literature using targeted websites. We identified no cost-effectiveness studies from our targeted search.

In summary, based on the findings of the CADTH report[1] and our own focused search, we identified no published studies on the cost-effectiveness of transcatheter valve-in-valve implantation for degenerated mitral or tricuspid bioprostheses.

Primary Economic Evaluation

No published economic evaluations were identified in the rapid response report[1] from the Canadian Agency for Drugs and Technologies in Health (CADTH) or in our targeted literature search. As well, the quality of the clinical evidence for transcatheter valve-in-valve implantation in the mitral position was low to very low (see Clinical Evidence section of this report), and this posed a challenge for developing an economic model. Of the studies included in the CADTH report,[1] only two retrospective cohort studies[25,26] had comparator arms, and both compared transcatheter mitral valve-in-valve implantation with surgery. As a result, their study populations did not include people who were considered inoperable or high-risk for surgery, which was the focus of our report. The clinical evidence for transcatheter valve-in-valve implantation in the tricuspid position was even more limited: no comparative studies were identified. Owing to these limitations, we did not conduct a primary economic evaluation.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding transcatheter valve-in-valve implantation for adults with degenerated mitral or tricuspid bioprosthetic valves who are considered inoperable or high-risk for surgery?

Context

People who initially received a mitral or tricuspid valve bioprosthetic valve may need to have it replaced, because the bioprosthesis can degenerate (it has an average lifespan of up to 15 years[43]), leading to heart failure.[1] Surgical replacement of a degenerated mitral or tricuspid bioprosthetic valve is the gold standard treatment. However, people who need valve replacement are often considered high-risk for another surgery because they have multiple comorbidities, and they instead receive only medical management (i.e., drug therapy, the current standard of care in Ontario).[24,42] An alternative approach to medical management for people who are high-risk for surgery is to insert a transcatheter heart valve into an existing degenerated mitral or tricuspid bioprosthesis; this is referred to as a transcatheter mitral valve-in-valve implantation (TMViV) or a transcatheter tricuspid valve-in-valve implantation (TTViV).[1] There are several issues related to the use of TMViV and TTViV in the current context and its potential implementation in the future:

- TMViV and TTViV are currently being performed in Ontario. To date, these interventions have been covered by philanthropic funds or hospital global budgets (CorHealth, phone communication, February 2021). No dedicated public funding has been allocated to these procedures
- Health Canada approved the Edwards Sapien 3 transcatheter heart valve in 2019 for people with "symptomatic heart disease due to a failing mitral surgical bioprosthetic valve (stenosed, insufficient, or combined) who are judged by a heart team to be at high or greater risk for open surgical therapy."[15] However, no device has been specifically licensed by Health Canada for transcatheter valve implantation in cases of degenerated tricuspid bioprostheses. At present, transcatheter valve-in-valve implantation in the tricuspid position is currently performed off-label[1]
- Although several access strategies are used for TMViV (i.e., transapical, transseptal, transatrial), the transseptal approach is preferred because it is less invasive and could be associated with better outcomes.[24] This technique allows the catheter to go through the femoral vein, has the advantage of a totally percutaneous approach, and avoids the need to enter the thoracic cavity or pericardial space.[24] However, this approach is more technically challenging.[44] It is therefore likely that delivery of this procedure will be limited to centres that already perform transcatheter valve-in-valve implantation and have existing mitral programs, where the transseptal approach is most frequently performed. In contrast, TTViV is done via either the femoral vein or the jugular vein and does not require a transseptal puncture (H. Wijeysundera, MD, phone communication, February 2021)

Methods

Analytic Framework

We estimated the budget impact of publicly funding transcatheter valve-in-valve implantation using the cost difference between two scenarios: (1) current clinical practice without dedicated public funding for transcatheter valve-in-valve implantation in adults with degenerated mitral or tricuspid valve bioprostheses (the current scenario) and (2) anticipated clinical practice with dedicated public funding for transcatheter valve-in-valve implantation in adults with degenerated mitral or tricuspid valve bioprostheses (the new scenario). Figure 1 presents the budget impact model schematic.

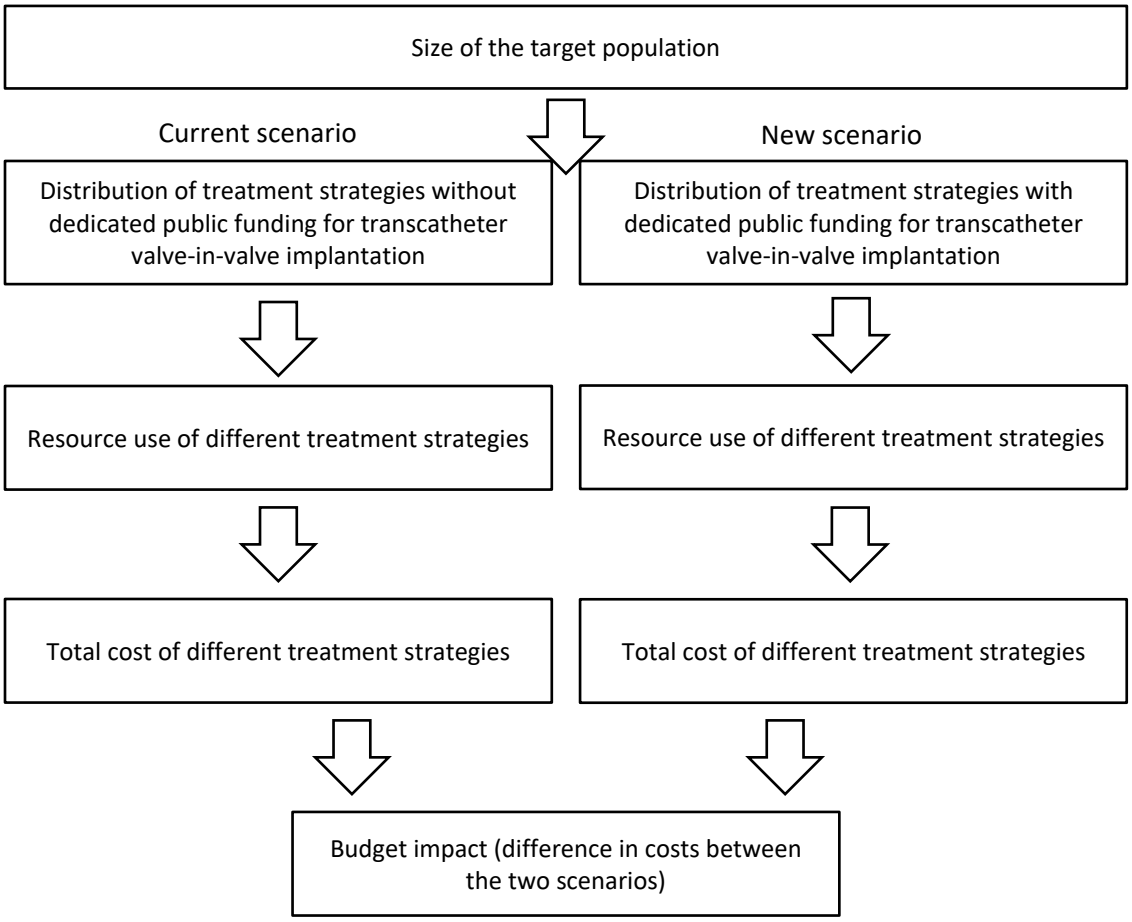

Figure 1: Schematic Model of Budget Impact

Key Assumptions

- We assumed that the health care resource costs associated with transcatheter valve-in-valve implantation would be similar for adults with degenerated mitral and tricuspid bioprostheses. Given that more evidence and data are available for adults with degenerated mitral bioprostheses and that the expected annual volume of TTViV in Ontario is small (i.e., fewer than five per year), we applied the costs for TMViV to both indications

- Adults who receive transcatheter valve-in-valve implantation would experience stable health conditions; adults who receive medical management (standard care) would experience gradually deteriorating health conditions that would require increased use of health care resources
- We assumed that there would be no significant cost differences related to the size of the replacement valve, the brand of the initial bioprosthetic valve, or the mode of bioprosthesis failure (i.e., stenosed, insufficient, or combined)

Target Population

Based on the findings of the clinical evidence review, our target population was adults with degenerated mitral or tricuspid valve bioprostheses who were considered inoperable or high-risk for surgery. The standard of care for these people is medical management because they are poor candidates for open-heart surgery—the gold standard for treatment of failing bioprostheses.[24,42] Although our target population was people who were inoperable or high-risk for surgery, this group was considered well enough to benefit from transcatheter valve-in-valve implantation.

It was not straightforward to accurately estimate the size of the population eligible for TMViV and TTViV in Ontario, because we were unable to obtain incidence data for our target population from the published literature. Instead, we focused on estimating the potential volumes of TMViV and TTViV over 5 years under dedicated public funding.

However, we could not reliably derive historical volumes from administrative databases for this intervention in Ontario (for degenerated mitral or tricuspid valve bioprostheses), for several reasons. First, the Canadian Classification of Health Intervention (CCI) code for TMViV was newly added to the Canadian Coding Standards for Version 2018,[45] which was released to replace the previous version at the start of fiscal year 2018/19. At about the same time, in 2019, Health Canada approved the Edwards Sapien 3 device for failing mitral valve bioprostheses.[15] Before these two recent developments, TMViV was performed off-label. As a result, it is unlikely that all cases of TMViV were assigned the new code in administrative datasets submitted to Canadian Institute for Health Information (CIHI) databases. As well, TTViV has no CCI code or Health Canada approval at present.

Therefore, we consulted with clinical experts to estimate potential future volumes of TMViV and TTViV. Based on expert consultations, we projected 25 cases of TMViV and one case of TTViV in year 1, increasing to 29 cases of TMViV and two cases of TTViV in year 5 (H. Wijeysundera, MD, phone communication, February 2021; Table 14).

Table 14: Projected Volumes of Transcatheter Valve-in-Valve Implantation for People With Degenerated Mitral or Tricuspid Valve Bioprostheses

Target population	Year 1	Year 2	Year 3	Year 4	Year 5
All degenerated valve bioprostheses	26	27	29	30	31
Degenerated mitral valve bioprostheses	25	26	27	28	29
Degenerated tricuspid valve bioprostheses	1	1	2	2	2

Source: H. Wijeysundera, MD, phone communication, February 2021.

Current Intervention Mix

As previously described, TMViV and TTViV are being performed in Ontario, but there is no dedicated public funding for these two indications (CorHealth, phone communication, February 2021). The purpose of the present analysis was to estimate the budget impact of dedicated public funding for TMViV and TTViV, compared to no dedicated public funding. We assumed that transcatheter valve-in-valve implantation was not available for adults with degenerated mitral or tricuspid bioprostheses in the current scenario. We also assumed that all adults with failing mitral or tricuspid bioprostheses who were inoperable or high-risk for surgery received medical management (standard care).

Uptake of the New Intervention and New Intervention Mix

We assumed that TMViV and TTViV would replace medical management (standard care) for adults in Ontario with failing mitral or tricuspid bioprostheses who were inoperable or high-risk for surgery, but were well enough to be eligible for transcatheter valve-in-valve implantation. Given the low prevalence of failing mitral or tricuspid bioprostheses in the province, combined with existing infrastructure and technical expertise related to these procedures (i.e., both TMViV and TTViV have been performed in Ontario), as well as their potential to improve heart failure symptoms, we anticipated that all eligible individuals would undergo TMViV and TTViV if dedicated public funding were allocated.

Resources and Costs

We found no published Canadian economic studies that reported costs associated with TMViV or medical management (standard care) for people with degenerated mitral bioprostheses. Therefore, we performed a retrospective costing study using CIHI databases (IntelliHealth Ontario; https://intellihealth.moh.gov.on.ca/) to estimate the costs of TMViV and medical management (standard care) for our target population. A recent publication[46] used CIHI data to estimate the cumulative costs of surgical and transcatheter aortic valve replacement for people with severe aortic stenosis in Ontario. We used the same methodology[46] to estimate resource use and costs in our analysis. We have summarized our methods below; Appendix 2 provides further details of the methods we used to obtain our cost parameters.

Through the IntelliHealth Ontario portal, we searched the Discharge Abstract Database (DAD) to identify cases associated with the principal intervention of TMViV (CCI code 1.HU.90.GR-XX-L) from fiscal years 2018/19 to 2020/21 (note: the data for 2020/21 were incomplete). We identified 53 cases for this CCI code, associated with a number of different codes for the most responsible diagnosis. We limited our dataset to the following most responsible diagnoses: complications of cardiac and vascular prosthetic devices, implants, and grafts (which included failing bioprostheses; International Statistical Classification of Disease, 10th Revision, Canadian Version [ICD-10-CA] code T82) or nonrheumatic mitral disease (such as mitral valve insufficiency, prolapse, stenosis, or other; ICD-10-CA code I34). We found 35 cases (T82: 14 cases; I34: 21 cases) across seven hospitals in Ontario; in those cases, the procedures were performed using hospital global budget funding (CorHealth, phone communication, February 2021). Patients' baseline characteristics can be found in Appendix 2, Table A4.

We used the encrypted unique health numbers of our sample population (N = 35) to link the dataset across sectors (i.e., inpatient hospitalizations and ambulatory care) and over time to create person-specific longitudinal records of health service utilization. Because of challenges with data availability (see Appendix 2 for details), we focused on inpatient hospitalization (DAD) and ambulatory care (National Ambulatory Care Reporting System [NACRS]), excluding physician fees and drug costs in the reference

case. Unless otherwise specified, the reported costs represent those associated with inpatient hospitalization and ambulatory care only.

In the reference case, we accounted for 2-year costs of TMViV and medical management (standard care) in our 5-year budget impact analysis, to capture the cost difference between the two groups. After 2 years, we assumed that the TMViV and medical management (standard care) groups would incur the same costs. A schematic of this approach is presented in Figure 2. When estimating the annual budget impact, we included new patients in a given year and patients who had been treated in the previous year.

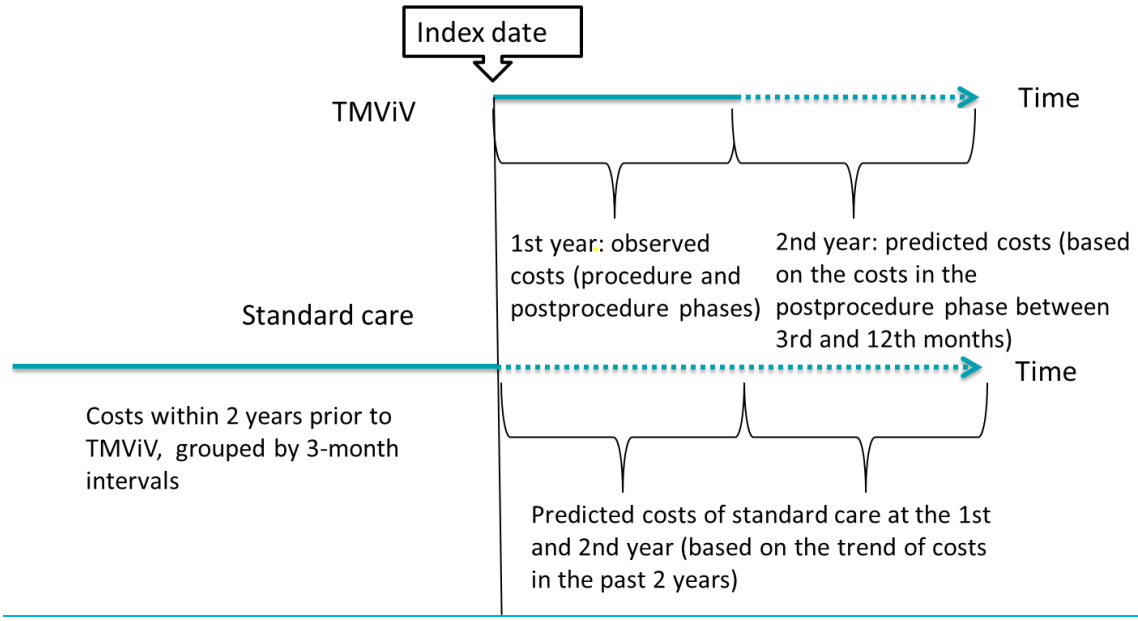

Figure 2: Cost Estimates for TMViV and Standard Care, Reference Case

Abbreviation: TMViV, transcatheter valve-in-valve implantation.

COST OF INTERVENTION

We used the admission date for TMViV inpatient hospitalization as the index date. We followed the 35 people in our dataset for 365 days after the index date, or until death. We defined two costing phases: the procedure phase, from date of the procedure to 60 days postprocedure; and the postprocedure phase, from 61 days to 365 days postprocedure. For each person, we summed the resource intensity weights (RIW) for inpatient hospitalization and ambulatory care visits over the two costing phases. We calculated the costs for each person from the RIWs in the corresponding phases and multiplied them by the province-specific cost per weighted case (i.e., cost of a standard hospital stay), which was $5,484 in Ontario in 2018/19.[47] We adjusted this cost to 2021 Canadian dollars in our analysis, using the Health and Personal Care Consumer Price Index.[48] We estimated that the average per-person costs in the procedure and postprocedure phases were $30,508 (inpatient hospitalization $29,982; ambulatory care $527) and $4,974 (inpatient hospitalization $4,294; ambulatory care $680), respectively. Compared to people with severe aortic stenosis, the average inpatient hospitalization costs in the procedure phase of TMViV were higher ($29,982 vs. $26,048).[46] This finding was considered reasonable (H. Wijeysundera, MD, email communication, May 2021). Further details are provided in Appendix 2, Table A5. Overall, the

average total cost was $35,482 for people treated with TMViV in the first year after the procedure (Table 15).

In the second year after the procedure, we assumed that people treated with TMViV would incur the same average monthly cost as they did during the postprocedure phase (61 days to 1 year). We were not able to obtain survival data for our sample population because vital statistics on death were available only up to calendar year 2015 in the IntelliHealth Ontario portal. Instead, we relied on published literature to estimate the average survival duration in year 2. Using DigitizeIt,[49] we extracted data points from a Kaplan–Meier curve in Simonato et al.[19] Based on the extracted survival data, the probabilities of survival by the end of the second month, first year, and second year after TMViV were 0.92, 0.86, and 0.8, respectively. We estimated that the mean survival time between 3 and 12 months was 8.9 months (0.86 × 10 + [0.92 − 0.86] × 5). We then calculated that the average monthly cost was $559 ($4,974 ÷ 8.9). Next, we estimated that the average survival time of the entire cohort in the second year was 9.96 months (0.8 × 12 + [0.86 − 0.8] × 6). After accounting for mortality, the average cost of the entire TMViV cohort was $5,566 ($559 × 9.96) in year 2.

COST OF MEDICAL MANAGEMENT (STANDARD CARE)

It was not straightforward to identify a comparison group that was similar to the intervention group using administrative data. Therefore, we used predictive analysis based on the costs incurred by people in our dataset before the index date to determine the cost of medical management (standard care). Specifically, we collected costs in 3-month (or quarterly) intervals for each person from 2 years to 1 day before the index date. We obtained eight observations for each person and a total of 280 observations from 35 patients (35 × 8). We used a linear mixed model to account for correlation due to repeated measurements of cost data, and we predicted the costs for the next eight quarters (or 2 years after the index date). We found a trend of increasing costs over time, possibly reflecting increasing health care resource use associated with disease progression. After controlling for age, sex, and main diagnosis in our prediction model, the mean cost increase was $470 per quarter. After adjusting for mortality, the mean predicted costs in the medical management (standard care) group in year 1 and year 2 were $21,884 and $25,836, respectively (Table 15). Further details of our prediction model can be found in Appendix 2.

OTHER CONSIDERATIONS

The Edwards Sapien 3 transcatheter heart valve was reported to cost $25,000 (the listing price in 2019 Canadian dollars) in a recent Canadian publication.[50] We expected that the device would likely be purchased by hospitals at a discounted rate. Because of the proprietary nature of this information, we were unable to ascertain an estimate of the actual device cost. However, we expected that estimating costs using the CIHI RIW system would allow us to capture actual device costs, even though we were unable to explicitly break down this cost component in our data.

Sunner et al,[46] the population-based retrospective cohort study on which we based our methodology, conducted person-level costing using health care utilization data (i.e., the CIHI RIW system) to obtain the full trajectory of costs associated with treating people who had severe aortic stenosis. In their approach, they also did not include the transcatheter heart valve system as a separate cost component to avoid double-counting the device cost. Overall, the procedure-phase costs (excluding physician fees and drug costs) associated with transcatheter valve replacement in our study and in Sunner et al[46] were comparable ($30,508 vs. $26,552). The relatively higher procedure-phase cost in our analysis may have

reflected the complexity and increased comorbidity associated with our target population, which was at higher risk than the population in Sunner et al.[46]

Furthermore, using the provincial-level cost for hospital stays, we were able to estimate costs that could be generalized across Ontario. However, it should be noted that the cost of a standard hospital stay varies across hospitals. In particular, hospitals that perform TMViV fall into the category of academic health sciences centres, which may have higher costs for a standard hospital stay than the provincial-level cost.[47] Nevertheless, based on administrative data, we determined that the hospital-specific cost of a standard hospital stay at the centres that have performed TMViV was only about 10% higher than the provincial-level cost (data not shown). We anticipated that using a hospital-specific cost for a standard hospital stay would result in cost savings similar to our reference case and would not substantially affect the overall budget impact.

All costs were adjusted to 2021 Canadian dollars, using the Health and Personal Care Consumer Price Index.[48] No discounting was applied.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represented the analysis with the most likely set of input parameters and model assumptions. When estimating the annual budget impact, we included new patients in a given year, and those who had been treated in the previous year. For example, to calculate the budget impact of publicly funding TMViV and TTViV in year 3 of our reference case, we included costs associated with the 29 new patients in year 3, and the 27 patients who had been treated in year 2. Based on this approach, the total cost of the new scenario would be $1.18 million ($35,408 × 29 + $5,566 × 27), and the total cost of the current scenario would be $1.33 million ($21,884 × 29 + $25,836 × 27).

Our scenario analyses explored how the results would be affected by varying input parameters and model assumptions. The cost inputs in our reference case and scenario analyses are presented in Table 15. We conducted eight scenario analyses:

- Scenario 1: Using observed costs and accounting for 1-year costs of TMViV and medical management (standard care) only
- Scenario 2: Accounting for physician fees and drug costs as part of total health care costs for the TMViV group and the medical management (standard care) group
- Scenario 3: Estimating the cost of TMViV after limiting our dataset to cases with the most responsible diagnosis of nonrheumatic mitral disease only (ICD-10-CA code I34; n = 21). Costs for medical management (standard care) were the same as in the reference case
- Scenario 4: Estimating health care resource costs using the Canadian national-level cost of a standard hospital stay ($6,162 in 2018/19)[47] instead of the Ontario provincial-level cost of standard hospital stay in the reference case
- Scenario 5: Assuming a 25% decrease in medical management (standard care) costs in years 1 and 2; we kept the costs of TMViV same as those in the reference case

- Scenario 6: Accounting for low- and high-cost scenarios for TMViV and TTViV, at 75% and 125% of the reference case costs, respectively; the cost of medical management (standard care) was unchanged in this scenario
- Scenario 7: Assuming annual volumes of TMViV and TTViV were double that of the reference case
- Scenario 8: Accounting for TMViV procedure-phase costs only (from the procedure date to 60 days postprocedure); costs associated with the TMViV postprocedure phase were excluded in this scenario

The methods used for scenarios 1, and 2 are further detailed below: Further details on the cost parameters for scenarios 2, 3, and 4 can be found in Appendix 2, Table A6.

SCENARIO 1: USING OBSERVED COSTS IN 1-YEAR TIME HORIZON

It was difficult to verify the reliability of the predicted costs used in the reference case (i.e., the predicted costs of TMViV in year 2 and the predicted costs of medical management [standard care] in years 1 and 2), although the observed trends (i.e., cost increase over time in the medical management [standard care] group) were considered reasonable. This was because of a lack of information on the long-term clinical (e.g., survival) and economic implications of TMViV compared to medical management (standard care). In addition, adults with degenerated mitral or tricuspid bioprostheses typically have multiple comorbidities,[24,42] which may require different levels of health care resource use. As a result, a high level of uncertainty was associated with estimating the long-term costs of TMViV.

To address this uncertainty, we limited our costs to 1 year in scenario 1 and assumed that both the TMViV and medical management (standard care) groups would acquire the same health care costs after 1 year. A schematic of this approach is presented in Figure 3. We based the 1-year costs for the TMViV group on health care resource use for inpatient hospitalization (i.e., DAD) and ambulatory care (i.e., NACRS) from our sample data of 35 cases. We used a self-controlled case series design to estimate the cost of the medical management (standard care) group. The self-controlled case series design allowed the people in our analysis to act as their own controls.[51] We assumed that the costs associated with inpatient hospitalizations and ambulatory care visits in the 1 year before the index hospitalization could be used to approximate the annual costs associated with standard care (H. Wijeysundera, MD, phone communication, February 2021). However, this approach may have underestimated the actual cost of medical management (standard care), given that the frequency of hospitalizations and emergency department visits would be expected to increase as mitral disease progressed without intervention (H. Wijeysundera, MD, email communication, April 2021).

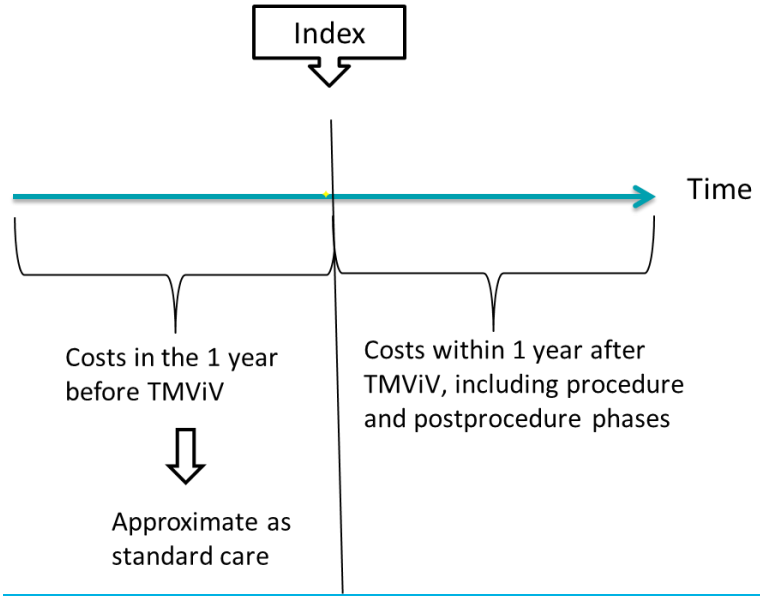

Figure 3: Costs Estimates for TMViV and Standard Care, Scenario 1

Abbreviation: TMViV, transcatheter valve-in-valve implantation.

SCENARIO 2: ACCOUNTING FOR PHYSICIAN FEES AND DRUG COSTS IN TOTAL HEALTH CARE COSTS

In this scenario, we accounted for physician fees and drug costs based on data reported in Sunner et al.[46] They found that in a referral phase (60 days before procedure to date of procedure), a procedure phase (date of procedure to 60 days postprocedure) and a postprocedure phase (61 days to 1 year postprocedure), acute care accounted for 75%, 78%, and 61%, respectively, of the total costs (i.e., [inpatient hospitalization cost (DAD) + total emergency room cost + same day surgery (NACRS)]/total cost) for people with severe aortic stenosis referred for transcatheter aortic valve replacement. The remaining costs consisted largely of physician fees and drug costs.[46]

For our analysis, we assumed that the cost of acute care for the medical management (standard care) group, and for the procedure and postprocedure phases of the intervention group, would constitute the same percentages of the total health care costs as those found in the referral, procedure, and postprocedure phases in Sunner et al.[46] To account for physician fees and drug costs, we divided the total costs for inpatient hospitalization and ambulatory care in the medical management (standard care) group, the procedure phase, and the postprocedure phase by their respective percentages of total health care costs.

Table 15: Budget Impact Analysis Inputs, Costs of Standard Care and TMViV

Input	Standard care, $	TMViV, $
Reference case		
Cost in year 1	21,884	35,482
Cost in year 2	25,836	5,566
Scenario 1: Using observed costs and accounting for 1-year costs of TMViV and standard care only		
Cost	16,102	35,482
Scenario 2: Accounting for physician fees and drug costs		
Cost in year 1	29,085	47,245
Cost in year 2	34,338	9,061
Scenario 3: Limiting the dataset to cases with the most responsible diagnosis of nonrheumatic mitral disease only (ICD-10-CA code I34) for TMViV[a]		
Cost in year 1	21,884	35,794
Cost in year 2	25,836	6,713
Scenario 4: Using the Canadian national-level cost of a standard hospital stay		
Cost in year 1	24,590	39,869
Cost in year 2	29,031	6,255
Scenario 5: Assuming a 25% decrease in standard care costs in years 1 and 2		
Cost in year 1	16,413	35,482
Cost in year 2	19,377	$5,566
Scenario 6: Accounting for low- and high-cost scenarios for TMViV		
6-1: TMViV cost 25% less than reference case in year 1	21,884	26,612
6-1: TMViV cost 25% less than reference case in year 2	25,836	4,175
6-2: TMViV cost 25% more than reference case in year 1	21,884	44,353
6-2: TMViV cost 25% more than reference case in year 2	25,836	6,958
Scenario 7: Assuming annual volumes of TMViV and TTViV were double that of the reference case		
Cost	Same as reference case	
Scenario 8: Accounting for TMViV procedure-phase costs only (procedure date to 60 days postprocedure)		
Cost	0	30,508

Abbreviations: ICD-10-CA, International Statistical Classification of Disease, 10th revision, Canadian version; TMViV, transcatheter mitral valve-in-valve implantation; TTViV, transcatheter tricuspid valve-in-valve implantation.

[a]We conducted this scenario to further restrict our ICD-10-CA code to a narrower population and reduce the odds of including people who were outside our population of interest but may have been captured because of various factors, such as coding errors. However, this scenario resulted in a smaller sample population, which increased the uncertainty of the analysis.

Results

Reference Case

Table 16 presents the projected total costs over 5 years for the current scenario and the new scenario in our reference case. Publicly funding TMViV and TTViV would result in a budget increase of $0.35 million in year 1, and then lead to annual cost savings from year 2 to year 5. Based on the assumption that the costs of medical management (standard care) would increase steadily with the progression of disease, the cumulative 2-year costs of medical management (standard care) were higher than that of TMViV ($47,720 versus $41,048). The total budget impact of publicly funding TMViV and TTViV would lead to cost savings of $0.33 million over the next 5 years.

Table 16: Budget Impact Analysis Results, Reference Case

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario (standard care)	0.57	1.26	1.33	1.41	1.45	6.02
New scenario (TMViV and TTViV)	0.92	1.10	1.18	1.23	1.27	5.70
Budget impact[b,c]	**0.35**	**−0.16**	**−0.15**	**−0.18**	**−0.19**	**−0.33**

Abbreviations: TMViV, transcatheter mitral valve-in-valve implantation; TTViV, transcatheter tricuspid valve-in-valve implantation.

[a]In 2021 Canadian dollars.

[b]Negative costs indicate savings.

[c]Some numbers may appear inexact due to rounding.

Sensitivity Analysis

Table 17 summarizes the results of the eight scenarios in our sensitivity analyses. Notably, when we used cost parameter inputs from observed data only, accounting for only 1-year costs for the TMViV and medical management (standard care) groups (scenario 1), the new scenario was associated with higher annual costs than the current scenario; the total 5-year budget impact was an increase of $2.77 million. When we accounted for physician fees and drug costs in the total health care costs (scenario 2), the budget impact was a marginally smaller cost savings of $0.23 million over 5 years compared to the reference case.

Overall, key factors driving the budget impact were the costs associated with TMViV and standard care, and the projected volume or size of the target populations for TMViV and TTViV. In most scenarios, we found that publicly funding TMViV and TTViV led to cost savings. In scenarios 1, 5, 6-2, and 8, we found a relatively small total budget increase of less than $5 million over the next 5 years.

Table 17: Budget Impact Analysis Results, Sensitivity Analyses

Scenario	Budget impact, $ million[a,b,c]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Reference case						
Budget impact	0.35	−0.16	−0.15	−0.18	−0.19	−0.33
Scenario 1: Using observed costs and accounting for 1-year costs of TMViV and standard care only						
Current scenario (standard care)	0.42	0.43	0.47	0.48	0.50	2.30
New scenario (TMViV and TTViV)	0.92	0.96	1.03	1.06	1.10	5.07
Budget impact	0.50	0.52	0.56	0.58	0.60	2.77
Scenario 2: Accounting for physician fees and drug costs						
Current scenario (standard care)	0.76	1.68	1.77	1.87	1.93	8.01
New scenario (TMViV and TTViV)	1.23	1.51	1.61	1.68	1.74	7.77
Budget impact	0.47	−0.17	−0.16	−0.19	−0.20	−0.23
Scenario 3: Limiting the dataset to cases with the most responsible diagnosis of nonrheumatic mitral disease only (ICD-10-CA code I34) for TMViV						
Current scenario (standard care)	0.57	1.26	1.33	1.41	1.45	6.02
New scenario (TMViV and TTViV)	0.93	1.14	1.22	1.27	1.31	5.87
Budget impact	0.36	−0.12	−0.11	−0.14	−0.14	−0.15
Scenario 4: Using the Canadian national-level cost of a standard hospital stay						
Current scenario (standard care)	0.64	1.42	1.50	1.58	1.63	6.77
New scenario (TMViV and TTViV)	1.04	1.24	1.33	1.38	1.42	6.40
Budget impact	0.40	−0.18	−0.17	−0.20	−0.21	−0.37
Scenario 5: Assuming a 25% decrease in standard care costs in year 1 and 2						
Current scenario (standard care)	0.43	0.95	1.00	1.05	1.09	4.52
New scenario (TMViV and TTViV)	0.92	1.10	1.18	1.23	1.27	5.70
Budget impact	0.50	0.16	0.18	0.17	0.18	1.18
Scenario 6-1: Accounting for a low-cost scenario for TMViV and TTViV (75% of the reference case)						
Current scenario (standard care)	0.57	1.26	1.33	1.41	1.45	6.02
New scenario (TMViV and TTViV)	0.69	0.83	0.88	0.92	0.95	4.27
Budget impact	0.12	−0.44	−0.45	−0.49	−0.50	−1.75
Scenario 6-2: Accounting for a high-cost scenario for TMViV and TTViV (125% of the reference case)						
Current scenario (standard care)	0.57	1.26	1.33	1.41	1.45	6.02
New scenario (TMViV and TTViV)	1.15	1.38	1.47	1.53	1.58	7.12
Budget impact	0.58	0.12	0.14	0.13	0.13	1.10
Scenario 7: Assuming annual volumes of TMViV and TTViV were double that of the reference case						
Current scenario (standard care)	1.14	2.53	2.66	2.81	2.91	12.05
New scenario (TMViV and TTViV)	1.85	2.21	2.36	2.45	2.53	11.39
Budget impact	0.71	−0.32	−0.31	−0.36	−0.37	−0.65

Scenario	Budget impact, $ million[a,b,c]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario 8: Accounting for TMViV procedure-phase costs only (procedure date to 60 days postprocedure)						
Current scenario (standard care)	0	0	0	0	0	0
New scenario (TMViV and TTViV)	0.79	0.82	0.88	0.92	0.95	4.36
Budget impact	0.79	0.82	0.88	0.92	0.95	4.36

Abbreviations: TMViV, transcatheter mitral valve-in-valve implantation; TTViV, transcatheter tricuspid valve-in-valve implantation.

[a] In 2021 Canadian dollars.

[b] Negative costs indicate savings.

[c] Some numbers may appear inexact due to rounding.

Discussion

Publicly funding TMViV and TTViV led to cost savings over the next 5 years, but it was unclear whether these savings could be translated directly to monetary benefit. We expect that potential cost savings would be attributable to improved efficiencies in health care resource utilization rather than direct budgetary savings.

Furthermore, the assumption underlying our reference case analysis was that people who received medical management (standard care) would experience gradually deteriorating health conditions that required increasing health care resource use over time, and those who received transcatheter valve-in-valve implantation would experience stable health conditions. Our budget impact analysis may yield different results if this assumption does not hold. However, the annual volumes of TMViV and TTViV are relatively small. We do not expect the budget impact results to differ substantially, as reflected in the two scenarios we conducted that did not apply this assumption (scenarios 1 and 8). These two found that although publicly funding transcatheter valve-in-valve implantation for adults with degenerated mitral and tricuspid bioprostheses led to a budget increase over the next 5 years rather than a cost savings, the total budget impact remained relatively small (< $5 million).

Finally, we identified adults with degenerated mitral or tricuspid bioprostheses who were considered inoperable or high-risk for surgery as the appropriate comparison group in our analysis. However, existing comparative studies evaluated TMViV compared to valve replacement surgery rather than medical management.[25,26] If our comparison group were not restricted to those who were high-risk for surgery, then we would expect the projected volumes of TMViV and TTViV under dedicated funding to be larger. We also conducted preliminary analyses using raw costing data from DAD (without adjusting for covariates) and found that the mean cost of surgery for biological valve replacement was higher than that of TMViV (data not shown). Publicly funding TMViV and TTViV for adults with degenerated mitral or tricuspid bioprostheses with no restriction on surgical risk may result in greater cost savings.

Strengths and Limitations

Our analysis had a number of strengths:

- It was based exclusively on Ontario data. As a result, our findings provide important local insight into the projected costs of publicly funding TMViV and TTViV for the province

- Each of our assumptions and model parameters achieved face validity independently from clinical experts
- Our use of the CIHI RIW system is a common approach for estimating health care costs based on person-level utilization data, with age- and comorbidity-weighted cost estimates[52]
- By deriving our costs from a prediction model, we were able to account for the trend of increasing costs associated with the progression of degenerated mitral valve bioprostheses under standard care, which has been observed in clinical practice (H. Wijeysundera, MD, email communication, March 2021)

However, our analysis also had several limitations:

- The lack of administrative and published data on adults with degenerated tricuspid bioprostheses led us to extrapolate our findings for adults with degenerated mitral bioprostheses to this indication as well
- Because the dataset we used was based on a small number of patients (35 TMViV patients; 24 of 35 with 1-year follow-up), our cost parameters had wide 95% confidence intervals and therefore were not precise. Moreover, the costs for medical management (standard care) in our reference case were derived from a prediction model, which introduced greater uncertainty, particularly because of a lack of published costing data to validate our findings. We addressed this uncertainty by conducting a range of scenarios and found that overall, the total budget impact remained relatively small (< $5 million) over the next 5 years
- We used CCI and ICD-10-CA codes to identify the most appropriate cases for our analysis. However, people outside our population of interest (e.g., those who have undergone a mitral valve replacement rather than replacement of a bioprosthetic valve) may still have been included in our analysis. However, overall, the baseline characteristics of our sample population were crudely comparable to those of people with degenerated mitral bioprostheses in several published studies.[25,26] As a result, we did not expect this limitation to have a substantial effect on our reference case results
- We were unable to obtain incidence data on our target population from administrative databases or published literature. As a result, our projected annual volumes were based on expert opinion. We independently validated these numbers with our clinical experts
- Although our use of the CIHI RIW system allowed us to identify person-level health care resource utilization data, the use of some technologies (e.g., magnetic resonance imaging, computed tomography, and other imaging) may not have been captured using this approach.[52] As well, our reference case analysis did not include the cost of physician services or drugs dispensed. We did include these costs in one of our scenario analyses (scenario 4)

Conclusions

We estimated that publicly funding TMViV and TTViV in Ontario would lead to an annual budget increase of $0.35 million in year 1 and annual cost savings from year 2 to year 5 of $0.16 million to $0.19 million. We estimated the total budget impact over the next 5 years to be $0.33 million in cost savings.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of adults who have lived experience with transcatheter valve-in-valve implantation, as well as the preferences and perceptions of risk and decision-making in choosing (or potentially choosing) to undergo this procedure for themselves or family members.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[53-55] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people who underwent transcatheter valve-in-valve implantation in two ways:

- A review by Ontario Health of the quantitative evidence on patient preferences and values
- Direct engagement by Ontario Health with people who have experience with this procedure—or who may encounter this procedure—through interviews

Quantitative Evidence

Research Question

What is the relative preference of patients for transcatheter valve-in-valve implantation compared with medical management (standard care, i.e., drug therapy) for the treatment of adults with degenerated bioprosthetic valves and who are considered inoperable or high-risk for surgery?

Methods

We did not undertake a literature search due to the expedited nature of this report. Instead, we undertook scoping of the literature and consultation with experts, and did not identify any studies that specifically addressed the preferences or values of patients who underwent transcatheter mitral valve-in-valve implantation (TMViV) or transcatheter tricuspid valve-in-valve implantation (TTViV) for the

treatment of degenerated bioprosthetic valves and who were considered inoperable or high-risk for surgery.

Although it was not directly related to mitral or tricuspid valves, we identified one systematic review[56] that evaluated quantitative evidence related to patient preferences and values for valve replacement for aortic stenosis. We included this study because it might provide insight into the experiences of patients who undergo TMViV or TTViV. We summarized the results of the systematic review narratively and conducted no additional statistical analyses beyond those reported in the systematic review.

We did not critically appraise the included studies. The purpose of our literature survey was to gain a broad overview of the quantitative evidence on patient preferences and values.

Results

The systematic review by Heen et al[56] evaluated evidence that addressed patients' values, preferences and practical issues related to decisions about transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR) for aortic stenosis. The authors searched databases and grey literature up to June 2020. Included studies were those that reported on adults with aortic stenosis and elicited people's values and preferences about treatment. Excluded studies were those that reported on medical management or palliative care. Values and preferences were defined as "the relative importance patients placed on the outcomes" for treatment decisions.[56] The authors of the systematic review included both qualitative and quantitative studies, but we have focused on only quantitative evidence.

Heen et al[56] included two quantitative studies.[57,58] A summary of the results is shown in Table 18. Overall, there were limitations in almost all domains; the greatest concerns were about participant selection, outcome presentation, and data analysis.[56] The certainty of the findings ranged from low to very low.[56] The majority of studies assessed values and preferences based on a single intervention. The authors concluded that people's values and preferences varied related to the outcomes associated with TAVI or SAVR. To improve their health, people were willing to accept higher mortality risk than the current evidence suggests for either procedure. As well, people preferred minimally invasive procedures with a shorter hospital stay and recovery time.

Table 18: Results of Systematic Review—Quantitative Studies

Outcome	Study design (Number of participants)	Estimate of effect (mean ± SD unless otherwise stated)	GRADE	Interpretation
Mortality (30 days)	Adaptive swing weighting (N = 109[a])	Maximum acceptable increase in risk in exchange from SAVR to TAVI: 3.7 ± 3.0%[b]	Very low[c,d,e]	Risk willingness of trading a reduction in risk for a less invasive procedure was uncertain and highly variable
Mortality and lifetime aortic stenosis–related symptoms and concerns, n (%)[f]	Standard gamble (N = 429)	Median risk willingness: 25% (IQR 25%–50%) No risk (0%): 104 (23%) Low risk (0%–8%): 26 (6%) High risk (> 8%–50%): 224 (51%) Prohibitive risk (> 50%–95%): 68 (15%) Prohibitive risk (95%–100%): 17 (4%)	Low[c,d]	Risk willingness of trading a reduction in risk for full health with the procedure was highly variable among participants and across risk groups
Disabling nonfatal stroke (30 days)	Adaptive swing weighting (N = 110[a])	Maximum acceptable increase in risk in exchange from SAVR to TAVI: 6.7 ± 5.7%[b]	Very low[c,d,e]	Risk willingness of trading a reduction in risk for a less invasive procedure was uncertain and highly variable
Independence (30 days)	Adaptive swing weighting (N = 131[a])	Maximum acceptable reduction in benefit in exchange from SAVR to TAVI: 13.9 ± 11.8%[b]	Very low[c,d,e]	Risk willingness of trading an increase in independence for a less invasive procedure was uncertain and highly variable
Requirement for dialysis (1 year)	Adaptive swing weighting (N = 132[a])	Maximum acceptable increase in risk in exchange from SAVR to TAVI: 6.2 ± 5.6%[b]	Very low[c,d,e]	Risk willingness of trading a reduction in the requirement for dialysis for a less invasive procedure was uncertain and highly variable
New permanent pacemaker (1 year)	Adaptive swing weighting (N = 131[a])	Maximum acceptable increase in risk in exchange from SAVR to TAVI: 7.0 ± 5.7%[g]	Very low[c,d,e]	Risk willingness of trading a reduction in permanent pacemaker insertion for a less invasive procedure uncertain and highly variable
Time over which the procedure has been proven to work	Adaptive swing weighting (N = 131[a])	Maximum acceptable decrease in duration that procedure is known to work in exchange from SAVR to TAVI: 17.4 ± 16.9 years[g]	Very low[c,d,e]	Risk willingness of trading the expected duration or a new valve for a less invasive procedure was uncertain and highly variable

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; IQR, interquartile range; SAVR, surgical aortic valve replacement; SD, standard deviation; TAVI, transcatheter aortic valve implantation.

[a]The total sample size was 219 participants, but they were not presented with all outcomes.

[b]The minimum acceptable reduction in benefit in exchange for reducing invasiveness from "invasive" to "minimally invasive."

[c]Downgraded due to serious risk of bias.

[d]Downgraded due to serious imprecision.

[e]Downgraded due to serious indirectness.

[f]Numbers in each category do not total 429 because of overlap between the two prohibitive risk categories.

[g]The maximum acceptable increase in risk in exchange for reducing invasiveness from "invasive" to "minimally invasive."

Source: Heen et al, 2021.[56]

Discussion

We identified no quantitative evidence on patient preferences and values specific to those who had a degenerated mitral or tricuspid bioprosthetic valve and were considered inoperable or high-risk for surgery. We did identify a systematic review about patient values and preferences related to valve replacement for aortic stenosis.[56]

The authors of the systematic review[56] noted that none of the studies presented patients' values and preferences based on a comprehensive assessment of the beneficial and adverse outcomes related to SAVR versus TAVI, nor did any studies report patient preferences around the choice between TAVI and SAVR. Instead, studies focused on preferences for a selection of attributes in isolation. None of the studies addressed the lifelong management of the treatment of valve failure.[56]

The conclusions of the systematic review[56] were very similar to those reported by a previous Ontario Health report on TAVI in people with severe aortic valve stenosis at low surgical risk.[59] Because of a lack of preferences and values evidence for people with severe aortic valve stenosis at low surgical risk, the Ontario Health analysis focused on populations with unspecified risk levels or populations at mostly (or all) high risk, and primarily populations of elderly people. Ontario Health concluded that among those with aortic stenosis, most preferred the less invasive nature and the faster recovery time of TAVI versus SAVR, and people were satisfied with the TAVI procedure.[59] Because both of these reviews focused on a different patient population (people with aortic stenosis), their generalizability is limited for people eligible for TMViV or TTViV who have a degenerated mitral or tricuspid bioprosthetic valve and are considered inoperable or high-risk for surgery.

Conclusions

- We identified no quantitative evidence on patient preferences and values specific to those who have a degenerated mitral or tricuspid bioprosthetic valve and are considered inoperable or high-risk for surgery
- People who had aortic stenosis varied considerably in terms of their values and preferences for the outcomes associated with TAVI or SAVR
- People were willing to accept higher mortality risk than current evidence suggests for either procedure, although this evidence was of low to very low certainty
- People preferred minimally invasive procedures with a shorter hospital stay and recovery time

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with transcatheter valve-in-valve implantation and those of their families and other caregivers. We engaged people via phone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with heart valve replacement, as well as those of their families and caregivers.[60] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[61-64] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including CorHealth, to spread the word about this engagement activity and to contact people who had experience with general heart valve replacement surgery, family members, and caregivers, including those with direct experience of transcatheter valve-in-valve implantation.

Inclusion Criteria

We sought to speak with people who had lived experience of transcatheter tricuspid/mitral valve-in-valve implantation or who may seek out this treatment in the future. We also sought to speak with family members of people with this experience. Participants did not need to have direct experience with this procedure to participate.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

For this project, we spoke with nine people who had experience with heart valve replacement surgery, or were expecting to require this surgery, living in Ontario. We also spoke with one family member of a patient who had undergone valve replacement surgery. The breakdown of patients was as follows:

- Two patients waiting for initial valve replacement surgery
- Three patients with a bioprosthetic valve (open-heart procedure), managing medically
- Five patients who had undergone transcatheter valve-in-valve implantation

Participants were mostly from southern Ontario, but we also spoke with people from Thunder Bay, Ottawa, and Sault Ste Marie.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 3) if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 15 to 30 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[65] Questions focused on the impact of heart valve failure on the quality of life of people, their experiences with treatments to manage or treat heart valve failure, their experiences with transcatheter valve-in-valve implantation, and their perceptions of the benefits or limitations of this procedure. For family members and caregivers, questions focused on their perceptions of the impact of heart valve failure and treatments on the quality of life of the person with heart valve failure, as well as the impact of the person's health condition and treatments on the family members and caregivers themselves. See Appendix 4 for our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[66,67] We used the qualitative data analysis software program NVivo[9] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of heart valve failure and treatments such as transcatheter valve-in-valve implantation on the people with heart valve failure, family members, and caregivers we interviewed.

Results

HISTORY OF HEART VALVE CONCERNS

All participants we interviewed had experience with heart valve issues, or they were a family member of someone with heart valve issues. The heart conditions arose for various reasons. Several participants reported that they had been born with cardiac problems and that the degeneration of their heart valve was anticipated to be an issue in their lifetime. Others reported that issues with their heart valve arose more recently and were discovered unexpectedly, or were the result of a larger cardiac condition:

> *I had I guess what I would call a murmur in my heart back in … about 2004, I think. And they said it wasn't so bad, but then it got worse and I had a bypass done in 2007. But they didn't replace the valve then—they left it.*
>
> *I was born with what they call Ebstein disease; I had three things wrong with my heart.*
>
> *What they discovered was … that I had a birth defect. It's apparently very, very common, where I was born with only two flaps in my aortic valve … versus three, so the heart had to work much harder to push the blood through with only two flaps. So eventually that original aortic valve had to be replaced with a with a three-flap one to correct the original birth defect.*

Some participants had yet to undergo a valve replacement procedure; two interviewees had current cardiac medical conditions and had been informed by their physicians that valve replacement was in their future if their condition could not be managed medically:

> *I have moderate to severe chronic kidney disease as well. And so I'm not a good candidate for the normal surgical process. And I'm at the point now … I'm just huffing and puffing way too much. I see a cardiologist regularly and we're trying to manage this with medication if we can. But this [valve replacement] is one alternative that we've begun to discuss.*
>
> *I've had atrial fibrillation for a long time … over time, the condition has worsened. And for some time, the mitral valve has been flopping a bit, and there's been some regurgitation between chambers. And now the aortic valve is doing the same.*

BIOPROSTHETIC VALVES

Most of the participants we spoke with had undergone at least one procedure to replace a heart valve. All of those participants had received a bioprosthetic valve—bovine or pig—rather than a mechanical valve. These participants reported being generally aware that their bioprosthetic valve had a limited

lifespan and would eventually need to be replaced. However, this knowledge was not universal; some participants said that the degeneration of their bioprosthetic valve came as a surprise to them:

> *I was told at the time that it would probably last for about 10 years, and it's exactly what happened.*
>
> *I don't know whether they ever said that it would have to be replaced in so many years or not. But they said it wouldn't last as long as the other one [a mechanical valve], and I didn't have a big concern about that at the time.*
>
> *And at that time, they said that the expected life span of the valve was about 10 to 15 years on average … I go for an annual check with the cardiologists. They stress test, echo [echocardiogram], ECG [electrocardiogram] and you know, they keep telling me that it looks as good as the day they put it in. So we're hoping we can get 20 years out of it, but that might be a bit optimistic. But so far, so good.*

Participants also spoke about their decision-making process in choosing a bioprosthetic valve rather than a mechanical valve, knowing it would have a shorter lifespan. Some participants reported that the requirement for ongoing warfarin with a mechanical valve was a strong factor against it, as well as the sound a mechanical valve could produce:

> *So the conversation at the time was really about the benefits and drawbacks of both options that were available. And with the mechanical having to be on Coumadin or warfarin or some medication, and ongoing medication that had potentially more significant side effects was the deciding factor. I mean, [for] the surgery itself the risk factor was about the same, so it was really ongoing lifestyle [that was the deciding factor].*
>
> *The thing was that you had to take warfarin if you took the [mechanical valve] and I just didn't feel like taking that warfarin every day.*
>
> *Yes, they had told me that too; that I would hear clicking if we [got a mechanical valve]. I said "Oh my God, that would drive me nuts." So they said, "No, maybe for you we'll go with the pig valve." And the tissue anyway is closer to human tissue, so they said, "You know, we think that's best for you."*

Other participants claimed that the choice of the bioprosthetic valve over a mechanical valve was a decision made mostly by their health care providers and that they were comfortable with the decision:

> *The head cardiac surgeon in the [hospital] … because we had the best of the best, he recommended [the bioprosthetic valve] and we didn't hesitate or question. We just listened and said sure. It sounded like it had the potential, at least, to be the better alternative, so let's do it.*
>
> *It wasn't really me who chose it, it was more the surgeon, just because he said it was closer to human tissue. So he thought it would be the best one for me.*

Regardless of the decision-making process for choosing a bioprosthetic valve, it was the degeneration of the valve that led people to learn about the valve-in-valve surgical procedure.

WORSENING SYMPTOMS LEADING TO VALVE REPLACEMENT

Most participants reported developing worrying new symptoms or worsening of existing symptoms before they required valve-in-valve replacement. These symptoms included shortness of breath, increased fatigue, lethargy, and a decreased ability to perform daily activities:

> *I had to keep taking the nitro spray. I couldn't walk very far … and I curl! If I was sweeping, I'd have to take that thing [nitro spray] three or four times in an end. And the doctor didn't seem to think that was such a good idea.*

> *It's just I could feel everything in me, all the energy, just drained out. I knew it was my heart. I knew it was the valve again. It's like the oxygen-rich blood was not getting to my brain; I couldn't think straight. I was constantly in a fog.*

> *And I'll give you one symptom, one of the things that was going on with me building up to this. I was doing a huge amount of sleeping. I mean, I'd wake up and then I'd go back to bed. I would sleep at night, and then I would sleep practically all day. It was quite something, and so clearly there was something obviously very wrong.*

With the development of these symptoms and participants' history of heart issues, many reported knowing or assuming that it was their valve that was the ultimate cause. However, for a couple of participants, the presence of other health issues meant that they could not be sure a degenerating bioprosthetic valve was the cause of their symptoms. Others expressed surprise that their valve was an issue, not having noticed a large change in their condition:

> *I thought my angina was getting worse, but I guess it was the valve that was getting worse.*

> *No, I didn't notice anything. But they felt that when I was getting something done … because I couldn't walk very far … and I didn't have a lot of energy. I didn't put it down to the valve or anything, but I couldn't walk long distance or stuff at all.*

Ultimately, these symptoms were not manageable through medications or other means. Some participants reported trying to manage medically for a time, but their symptoms grew worse until it was clear that medical management would not be successful. For these participants, who had previously undergone a serious open-heart procedure and were now facing the potential of a second procedure to repair the valve a second time, there could naturally be a great deal of fear and anxiety. Some participants spoke of their concerns and worries that this new degeneration of their heart valve might be ultimately fatal:

> *I was losing weight; I lost 15 pounds. I wasn't hungry anymore. My anxiety level was way up high, mainly because I had a son at home and I was worried … If I die he's all alone—what's going to happen here, you know?*

> *So it really scared me and I just kind of put it in my head, well, I have to accept that this is it for me.*

Others reported that they were not as concerned and not too anxious about their new heart issues, having undergone numerous procedures and having dealt with these types of medical concerns for many years:

> *Oh sure, I was fine. I've had heart problems for a long time. I've had two open-heart surgeries, and I think I've had a couple of things done in the inside of the arteries and that too … Well, I wouldn't say "old hat," but you don't get as excited about things that's for sure. I'm 84 years old going on 85, so I've had a good life.*

TRANSCATHETER VALVE-IN-VALVE IMPLANTATION

Information About Treatment Options

The majority of participants had undergone one valve replacement procedure, and each of these procedures was an open-heart surgery. Participants were very familiar with the process and the recovery time for an open-heart procedure, although these surgeries had taken place 6 to 16 years prior to the interview. Each participant commented on the difficulty of that surgery—its long recovery time and challenging aftermath. Because of this, when they learned about the new degeneration of their bioprosthetic valve, participants were anxious about the potential need to undergo such an invasive procedure again:

> *I didn't feel like I could go through it. I didn't want another open-heart surgery. It was pretty bad. I had a hard time in 2013 with it. They had me in a coma for 5 days.*

> *[Open-heart surgery] was really something else. I just remember that, and it took me months and months to recuperate. It was the biggest surgery, and it was really scary [thinking of having a second open-heart surgery].*

Because of their fears about another open-heart surgery, participants reported that they were generally pleased when they heard about the transcatheter valve-in-valve procedure and its potential as a less invasive solution. They felt that the potential for a shorter recovery time and less time spent in hospital were both beneficial aspects of the procedure. Information about the procedure generally came from their cardiologists or surgeons, and participants were happy with the discussions and decision-making that took place:

> *[The doctor] talked to me about [the transcatheter procedure] and then, when I went down to see how it's done and everything … I liked the idea. It would just be for the 1 day, and that's it. No open-heart, and that was pretty interesting.*

> *I said no, I'm too scared, I'm not going through what I went through before. But they said, "But it won't be open-heart, so it won't be the same thing. It's less invasive, you should recuperate a lot faster." Anyway, they gave me all the details and like I said, at first I said no … Anyway, after maybe a month of thinking about it, I said yes let's go, I want this, because this is my last option.*

Some participants knew of this procedure from family experience or from friends or colleagues; knowing others who had undergone a transcatheter surgical procedure to repair a heart valve was a good source of information about the procedure and its status in Canada:

> *I know because my mom had this … and two of her sisters also had it. I know about the transcatheter TAVI procedure, and I know that currently in Canada at least … it's still only used for people who would have a hard time surviving open-heart surgery.*

> *We do know someone else that did get [the transcatheter valve-in-valve implantation] procedure in Toronto, and he's also doing very well, and he's very grateful he didn't have to have the open-heart method.*

Even people who had yet to undergo transcatheter valve-in-valve implantation reported positively about its potential. Although these people still had functioning bioprosthetic valves, they were aware that the valves had a limited lifespan. Knowing that their valve would likely need to be replaced, people were hopeful that they would be a candidate for the less invasive transcatheter procedure rather than undergoing another open-heart surgery:

> *Oh certainly [we want a transcatheter procedure], because first of all, as my husband calls it, you don't get your chest cracked open, so there's far less healing and recovery time. It's just less pain, it's less invasive, less anesthetic, better outcome, I would hope.*

> *As a patient and a member of the public, besides being somebody who might have it, it doesn't really seem to make a whole lot of sense to me. Because when you think of what's involved in the two procedures that are a resource-intensive process for open-heart surgery versus transcatheter, and then the recovery time and follow-ups compared to the two of them for the patient and for the facilities … it doesn't really seem to make sense [to have an open-heart procedure].*

The Transcatheter Valve-in-Valve Procedure

Overall, participants who received the transcatheter valve-in-valve procedure reported that it was relatively straightforward and simple. Participants reported going into hospital on the day of the procedure and staying overnight or for a few days after for monitoring. Some reported mild discomfort at the incision in the groin area for the catheter, but they were generally pleased with the ease of the procedure:

> *I went in the hospital early in the morning. They did the pre-op thing for me, and then they just put whatever they did in your groin, they put the tube up. I was in the operating room, and they put the tube in, and it was over. It was pretty simple. The only thing I didn't like about it is I have a bad rotator cuff in my right arm and I had to keep it up and it was very uncomfortable. Other than that, there was nothing else wrong with it, it was pretty straightforward. It was easy.*

> *Oh I was in there overnight—that's it.*

> *They told me I'd be in the hospital for 7 days. Because of the incisions in the groin area, they had to wait till that started to heal before they let you out. After 5 days in the hospital they needed beds—there's always a bed shortage and everything. So they needed beds, and I was doing very well, I was able to walk, and so after 5 days they sent me home.*

The positive perspective of the transcatheter valve-in-valve procedure was especially stark when participants compared it to their previous open-heart surgery. They naturally tended to compare the two procedures, and they viewed the less invasive transcatheter procedure more favourably in terms of degree of pain, recovery, and outcome:

Yeah [I noticed a difference]: the pain. There's no pain from the surgery.

[Transcatheter] is far better than open-heart surgery. Oh, it's a lot better. You still worry about it but … they show you everything, and it's a lot easier on you. It's a lot easier on your body. It's a lot easier on your mind when you get it done. I just I think it's a lot better, the best way to do it.

To me personally, it went way better than I expected. Like I couldn't believe it. It saved my life.

After transcatheter valve-in-valve implantation, participants reported feeling a positive change almost immediately. Some reported feeling more energy and a rapid return of their ability to perform tasks and daily activities that had been compromised by their degenerating heart valve. Although home care was necessary for some people after the procedure, it was for only a limited time as they returned to better health. This improvement in health led to increased quality of life and a return to baseline function, with no noticeable side effects:

I would say in the next few days I felt considerably better. I had home care come in for a week here at the house.

This [transcatheter implantation], it was no problem. It's like a couple of days, and I felt really good with it. My breathing and everything was a lot better this time, and everything was great. Well, except I got another lot of other problems that went along with it, but other than that I still feel great with it, the heart part. That was no problem with recovery—it was good. It was easy.

And when I woke up, I felt a big difference immediately. There was no brain fog; that was gone. I felt this surge of energy that I didn't have for many years. It was really, really weird and spooky but, like, so wonderful.

I'm starting to walk that [route] without being affected at all. But there was the time when I couldn't do it, and it was just awful. So anyway, I'm feeling fabulous and I've had no negative results or anything of that sort.

Barriers to Procedure

Some participants mentioned having to overcome some barriers to receiving transcatheter valve-in-valve implantation. Because the procedure is performed only at certain hospitals, some people had to travel quite a distance to have it done. This could add logistical challenges to receiving the treatment, as well as an extra cost burden for travel or lodging. Participants also reported that they encountered some frustrating wait times, with cancellations and COVID-19-related delays. People who were located where these barriers were lower expressed gratitude and appreciation for having access to this procedure:

No, it took a little while. But then I was scheduled for it earlier, but then COVID, and they had to cancel it because of COVID, mainly. I was looking forward to getting it done because I didn't feel as good, and because once I knew it was that was the problem I wanted to get it done quickly. But I had to wait another 4 months, I think, from the first time they cancelled it. I had to wait another 4 months.

I'm lucky I'm in [this] area because there are so many hospitals here. But they kept postponing it. It had been postponed twice or three times. Number one, a shortage of nurses, and another time a shortage of beds. Another time, there were more people that were emergency surgeries. They

> *needed to go before me. And then the third time that they cancelled on me and said it's going to be postponed, well I just broke down on the phone.*

When considering the potential of a transcatheter procedure in their future, participants who had yet to have their bioprosthetic valve replaced expressed their willingness to travel to access the procedure, if necessary. They knew that the location of medical centres that provided the procedure could be a barrier, but this was not enough to prevent them from wanting to seek out this less invasive procedure:

> *Personally, I'd be willing to travel for you know … if you if it means the difference between having open-heart surgery and having a [transcatheter] procedure. I'd definitely be willing to travel within Ontario. It's not convenient, but it certainly it beats … you know, it's more convenient in terms of procedure, right? And it wouldn't be such a big deal about being laid up somewhere elsewhere outside of home, because it's not such a long period to be in hospital. It's not such a big recovery, and travelling afterwards wouldn't be such a big deal and all that kind of stuff.*

The family member of one participant interviewed expressed frustration that their loved one did not qualify for transcatheter valve-in-valve implantation. For medical reasons, this person was unable to have the transcatheter procedure to install the bioprosthetic valve and had to have an open-chest procedure instead. The family member expressed frustration at this and their hope that if the valve needed replacing in the future, transcatheter valve-in-valve implantation would be an option:

> *Well, I like that idea that they could go in and do the [transcatheter procedure] as a repair on something instead of open-heart. I would hope that my husband would be a candidate for that. If he was a suitable candidate, he would jump on the table for the [transcatheter procedure], absolutely.*

Discussion

Direct engagement allowed for the robust examination of patient preferences and values surrounding transcatheter valve-in-valve implantation for those with heart valve failure. All participants spoke extensively about the symptoms of heart valve failure and the negative impact these symptoms could have on their daily lives, including their ability to work and participate in regular daily activities.

Through direct engagement we were also able to speak to participants before and after transcatheter valve-in-valve implantation, allowing for a thorough exploration of decision-making factors and outcome preferences for treatment. Some participants were able to directly compare their transcatheter procedure with a previous open-heart surgery, as well as with medical management of their heart valve failure to understand the perceived benefits and drawbacks of transcatheter valve-in-valve implantation. Having direct lived experience with transcatheter valve-in-valve implantation, participants were also able to provide details of the procedure, recovery, and impact on their daily lives.

Participants were also able to speak about barriers they faced in accessing and choosing transcatheter valve-in-valve implantation, including geographic access issues. This context provides insight into the use of this procedure in the province and the potential effect on patients if they could access it more easily.

Direct engagement was somewhat limited by the relatively small number of people who have undergone transcatheter valve-in-valve implantation in Ontario. as well, a natural selection bias existed, in that those we spoke to were more likely to have had a positive, successful outcome from their

surgeries and were able to be selected to undergo transcatheter valve-in-valve implantation. We were unable to speak to people who could not receive transcatheter valve-in-valve implantation because of medical comorbidities or other factors.

Conclusions

Bioprosthetic heart valve failure is a serious medical condition that can cause a number of symptoms that negatively affect a person's quality of life. Through interviews, participants reported on these negative effects, as well as on their positive perception of transcatheter valve-in-valve implantation to repair a damaged heart valve and improve symptoms and quality of life. Participants valued the minimally invasive and quick recovery time associated with transcatheter procedures.

Preferences and Values Evidence Discussion

We obtained preferences and values evidence through an examination of quantitative evidence and through direct patient engagement. Each method examined the perspectives of patients on transcatheter valve-in-valve implantation and its potential effects on people with heart valve disease, including their quality of life.

Although the quantitative evidence was not directly related to TTViV or TMViV, its findings did align with the results of the direct engagement: people expressed a strong preference for procedures that were minimally invasive and that produced positive results with a short recovery time. During interviews, these were common themes expressed by people when they reflected on the transcatheter procedure or by those who expected to require valve replacement in their future.

Preferences and Values Evidence Conclusions

Bioprosthetic heart valve failure can cause a number of symptoms that negatively affect a person's quality of life. Through interviews, participants reported on these negative effects, as well as on their positive perceptions of transcatheter valve-in-valve implantation to repair the damaged heart valve and improve symptoms and quality of life. In the published literature and through direct engagement, people reported their preference for a minimally invasive transcatheter procedure with a quick recovery time.

Conclusions of the Health Technology Assessment

For adults with degenerated mitral or tricuspid bioprosthetic valves and who are considered inoperable or high-risk for surgery, transcatheter mitral valve-in-valve implantation (TMViV) or transcatheter tricuspid valve-in-valve implantation (TTViV): may reduce mortality, but the evidence is very uncertain; may reduce stroke, myocardial infarction, or other complications, but the evidence is very uncertain; and may improve NYHA functional class.

No studies compared TMViV or TTViV to medical management.

We did not identify any economic studies on TMViV or TTViV for degenerated mitral or tricuspid bioprostheses. We also did not conduct a primary economic evaluation because of uncertainty in the clinical evidence, so we were unable to determine the cost-effectiveness of transcatheter valve-in-valve implantation for adults with degenerated mitral or tricuspid bioprostheses who are considered inoperable or high-risk for surgery. We estimated that publicly funding TMViV and TTViV in Ontario would result in a cost saving of $0.33 million over the next 5 years. We attributed this cost saving to averted increases in health care resource use for those who receive transcatheter valve-in-valve implantation, because they would be expected to experience stable health conditions, compared to those who receive medical management (standard care), who would be expected to experience gradually deteriorating health conditions.

Bioprosthetic heart valve failure can cause a number of symptoms that negatively affect a person's quality of life. Through interviews, participants reported on these negative effects, as well as on their positive perceptions of transcatheter valve-in-valve implantation to repair the damaged heart valve and improve symptoms and quality of life. In the published literature and through direct engagement, people reported their preference for a minimally invasive transcatheter procedure with a quick recovery time.

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CCI	Canadian Classification of Health Interventions
CI	Confidence interval
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Database
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICD-10-CA	International Statistical Classification of Disease, 10th Revision, Canadian Version
NACRS	National Ambulatory Care Reporting System
NYHA	New York Heart Association
RIW	Resource intensity weight
SAVR	Surgical aortic valve repair
SD	Standard deviation
TAVI	Transcatheter aortic valve implantation
TMViV	Transcatheter mitral valve-in-valve implantation
TTViV	Transcatheter tricuspid valve-in-valve implantation

Glossary

Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Natural history of a disease	The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Time horizon	In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Appendices

Appendix 1: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Additional Observational Studies[b] (Downs and Black)

Criteria	Geurrero et al, 2021[18]	Simonato et al, 2021[19]
Aim described?	Yes	Yes
Outcomes described?	Yes	Yes
Patients described?	Yes	Yes
Intervention described?	Yes	Yes
Confounders described?	Not applicable	Not applicable
Findings described?	Yes	Yes
Estimates of the random variability?	Not applicable	Not applicable
Adverse events reported?	Yes	Yes
Lost to follow-up described?	Yes	Yes
Probability for main outcomes given?	Yes	Yes
Subjects asked representative?	Unable to determine	Unable to determine
Subjects participating representative?	Yes	Yes
Staff, facilities representative?	Unable to determine	Unable to determine
Subjects blinded?	No	No
Attempt to blind those measuring?	No	No
Was data dredging made clear?	No	No
Adjust for different lengths of follow-up?	Not applicable	Not applicable

Criteria	Geurrero et al, 2021[18]	Simonato et al, 2021[19]
Statistics for main outcomes appropriate?[c]	Yes	Yes
Compliance reliable?	Not applicable	Not applicable
Outcome measures valid and reliable?	Yes	Yes
Recruitment from same population?	Not applicable	Not applicable
Subjects recruited over same period?	Not applicable	Not applicable
Randomized?[d]	No	No
Adequate adjustment for confounding?	No	No
Loss to follow-up taken into account?	Not applicable	Yes

[a]Possible risk-of-bias levels: yes, no, unable to determine.
[b]Observational studies[18,19] not included in the Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review.[1]
[c]Rated as "Yes" for single-arm studies because descriptive statistics were used to report most outcomes, which was considered appropriate.
[d]The item on allocation concealment was deleted because neither of the studies used randomization.

Table A2: GRADE Evidence Profile for TMViV, Single-Arm Studies

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Mortality							
1 (systematic review)[a] 11 (observational)	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Stroke							
1 (systematic review)[a] 10+ (observational)[a]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Myocardial infarction							
1 (systematic review)[a] 6 (observational)	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
NYHA functional class							
1 (systematic review)[a] 11 (observational)	Serious limitations (−1)[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	Other considerations (+1)[e]	⨁⨁ Low
Complications							
1 (systematic review)[a] 9 (observational)	Serious limitations (−1)[b]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Hospital or intensive care unit stay							
1 (observational registry)	Serious limitations (−1)[f]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NYHA, New York Heart Association; TMViV, transcatheter mitral valve-in-valve implantation.

[a]Number of observational single-arm studies included in this outcome in the systematic review[24] was unclear.

[b]Retrospective, single-arm/registry studies with no comparator group. Not all studies used consecutive enrolment of patients. Loss to follow-up was unclear in some studies. Studies used different transcatheter access routes (e.g., transapical, transseptal, or both).

[c]Small sample size (11 of 12 TMViV single-arm studies had sample sizes of 60 patients or less).

[d]Although studies reported NYHA functional class at baseline and follow-up, only two studies[24,32] reported a formal statistical comparison of NYHA functional class before and after TMViV. It is unclear why the systematic review[24] reported fewer patients after TMViV than before TMViV (i.e., the before/after comparison included 57 patients before TMViV and 39 patients after TMViV).

[e]Upgrade because of the large effect size reported in studies that conducted a statistical comparison.

[f]Retrospective, observational registry study with no comparator group.

Table A3: GRADE Evidence Profile for TTViV, Single-Arm Studies

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Mortality							
4 (observational)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁ Very low
Stroke							
2 (observational)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very low
Myocardial infarction							
1 (observational)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[d]	Undetected	None	⨁ Very low
NYHA functional class							
4 (observational)	Serious limitations (−1)[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	Other considerations (+1)[f]	⨁⨁ Low
Complications							
3 (observational)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁ Very low
Hospital or intensive care unit stay							
No studies identified							

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NYHA, New York Heart Association; TTViV, transcatheter tricuspid valve-in-valve implantation.

[a]Single-arm studies, small sample sizes and no comparator group. Largest study[41] was a voluntary registry with patients lost to follow-up. "Although we solicited participation in the registry widely, invitations were not universally accepted, including a number of previously reported cases, and there were undoubtedly TVIV [transcatheter valve-in-valve] implantations of which we were unaware, which may introduce selection bias."

[b]Small sample size (two studies[39,40] had seven patients, one study[42] had five patients). Largest study[41] (N = 152) was a voluntary registry with patients lost to follow-up.

[c]Small sample size. Landes et al[40] reported on seven patients. Ruparelia et al[42] reported on five patients.

[d]Ruparelia et al[42] reported on five patients.

[e]Although all studies measured NYHA functional class at baseline and follow-up, only McElhinney et al[41] reported a statistical comparison of NYHA functional class before and after TTViV at 30 days and median follow-up of 13 months. McElhinney et al[41] reported statistically significant improvement in NYHA functional class. The three other studies[39,40,42] had very small sample sizes (each study had seven patients or less) with no statistical comparisons.

[f]Upgrade due to the large effect size reported in the study that conducted a statistical comparison.

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Appendix 2: Additional Details of Costing Study Methods and Results

Methods

DATA SOURCES

We used the Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS) from the Canadian Institute for Health Information (CIHI) for our costing study. We accessed these databases through IntelliHealth Ontario (https://intellihealth.moh.gov.on.ca/), a repository that houses clinical and administrative datasets from various sectors of the Ontario health care system. The DAD contains demographic and clinical data for inpatient care discharges in Ontario. The NACRS includes data for emergency department visits, day surgeries, and high-cost outpatient clinics. Both DAD and NACRS completed a refresh in quarter 2 of fiscal year 2020/21 (Oct 31, 2020). These data elements have been validated and were used in several costing studies[46,68,69] on transcatheter heart valve procedures in Ontario.

We identified data in the Medical Services database through IntelliHealth Ontario. However, data were available only from fiscal year 2018/19 or earlier. Because of the lack of recent data, we did not include physician fees in our analysis. Because the National Prescription Drug Utilization Information System was unavailable to us, we were unable to obtain information about drug claims made to the Ontario Drug Benefit program by our population of interest. For this reason, we also excluded drug costs from our analysis. Finally, we did not obtain costing data from databases other than DAD and NACRS, because previous publications have found that costs identified from other databases, such as Home Care and Complex Continuing Care Assessment, have made only minor contributions to the total health care costs incurred by people with baseline characteristics relatively similar to our target population (e.g., severe aortic stenosis). For instance, Sunner et al[46] reported that on average, the costs of inpatient hospitalization and ambulatory care accounted for 76.5% and 1.5% of the total health care costs, respectively, in the procedure phase (from the procedure to 60 days postprocedure) for transcatheter aortic valve replacement. The other main cost component was physician fees in the procedure phase, which accounted for 20.6% of total costs.

STUDY POPULATIONS

We searched DAD to identify adults who had the principal intervention of TMViV between fiscal years 2018/19 and 2020/21 using the Canadian Classification of Health Interventions (CCI) code 1.HU.90.GR-XX-L. The principal intervention is defined as the most significant treatment during hospitalization (note: the CCI code for TMViV has been available since 2018). In total, we identified 53 cases with this CCI code, associated with a number of different codes for most responsible diagnosis. The most responsible diagnosis is the one diagnosis that is the primary reason for a person's stay in hospital. We limited our dataset to the following most responsible diagnoses: complications of cardiac and vascular prosthetic devices, implants, and grafts (which include failing bioprostheses; International Statistical Classification of Disease, 10th Revision, Canadian Version [ICD-10-CA] code: T82) or nonrheumatic mitral disease (such as mitral valve insufficiency, prolapse, stenosis, or other; ICD-10-CA code: I34). We found 35 cases (T82: 14 patients; and I34: 21 patients) across seven hospitals in Ontario.

We used the information from the indexed hospitalization for the TMViV procedure to define patients' baseline characteristics (e.g., age and sex) and used the secondary diagnoses in the indexed hospitalization to define the comorbidities. This approach may have captured limited information about a patient's comorbidities. Using the postal code variable, we linked our dataset to Statistics Canada's Postal Code Conversion File to obtain information on neighbourhood income quintiles in Ontario.

OUTCOME DEFINITIONS

We used the admission date of inpatient hospitalization for TMViV as the index date. The primary outcome was the average cumulative health care costs of hospitalization and ambulatory visits for people treated with TMViV in three phases: the preprocedure phase (1 year prior to the index date), the procedure phase (from the index date to 60 days postprocedure), and the postprocedure phase (from 61 days to 1 year postprocedure). These distinct costing phases were meant to reflect clinically meaningful phases of treatment for failing bioprostheses in the mitral position. To identify appropriate costing phases, we referred to a recent Canadian costing study[46] on transcatheter aortic valve implantation. These phases were also considered appropriate for TMViV. (H. Wijeysundera, MD, email communication, March 2021)

We used encrypted unique health numbers to link datasets, and we created person-specific longitudinal records of health service utilization (i.e., baseline characteristics, hospitalizations, and ambulatory care visits) for the 35 cases in our dataset. For each person, we summed the resource intensity weights (RIW) for inpatient and ambulatory care visits over the three costing phases. We used the costing methodology as described in Wodchis et al[52] to calculate the RIWs in corresponding phases for each individual, which multiplied the province-specific cost per weighted case (i.e., cost of a standard hospital stay in Ontario[47]) by a person's RIW for a given hospitalization and/or ambulatory care visits. The RIW is a measure of resource utilization intensity developed by CIHI that classifies people with similar resource-use patterns into statistically and clinically homogeneous groups based on their clinical and administrative data profiles.[52] It is meant to reflect the average amount of hospital resources (such as administration, staff, infrastructure, technology) associated with someone who has a particular condition, relative to the average resource consumed by the typical patient.[52] The RIW is a relative weight value, and the RIW for an "average" inpatient case is 1. The cost of a standard hospital stay is the average cost for a hypothetical patient with a RIW of 1. The national-level cost of standard hospital stay was $6,162 in 2018/19,[47] and the provincial-level cost of standard hospital stay for Ontario was $5,484 in 2018/19.[70] We adjusted these costs to 2021 Canadian dollars in our analysis, using the Health and Personal Care Consumer Price Index.[48]

Finally, we also examined the numbers of hospitalizations and ambulatory visits in our dataset. In the present study, we did not include clinical outcomes.

STATISTICAL ANALYSIS

We summarized patient characteristics for the TMViV and medical management (standard care) groups using descriptive statistics: number and percentage for categorical or ordinal variables, and mean and standard deviation for continuous variables. We calculated two-sided 95% confidence intervals (CI) for mean costs and other outcomes in three phases using the simple bootstrap method (i.e., the lower 2.5th percentile and the upper 97.5th percentile of the bootstrap distributions).[71] All 35 patients received complete follow-up in the preprocedure and procedure phase, but only 24 patients went on to receive further follow-up in the postprocedure phase (i.e., patients who underwent TMViV prior to November 1, 2019). Therefore, our statistical analyses for the preprocedure and procedure phases were based on 35 patients, but those in the postprocedure phase were based on 24 patients. We calculated the average monthly costs in the preprocedure and postprocedure phases separately for these 24 patients, and we calculated the difference in monthly costs between these phases for each person.

We also predicted health care costs under the assumption that patients did not receive TMViV. We collected costs in 3-month (quarterly) intervals for each person from the 2 years to 1 day before the

index date. We had eight observations for each person, for a total of 280 observations from 35 patients (35 × 8 = 280). We used a linear mixed model to account for correlations due to repeated measurements of cost data, and we predicted costs for the next eight quarters (i.e., 2 years after the index date).

The predicted costs show the estimated cost trends over time for the entire population without accounting for mortality. However, because no mortality seemed unrealistic for this population, we adjusted the costs to reflect the fact that a proportion of patients would die during follow-up. We were unable to determine the natural history of disease for patients treated with medical management (standard care). Because there is no clinical evidence to show that TMViV improves survival compared to medical management (standard care), we assumed that the standard care and TMViV groups had the same mortality rates. The probabilities of survival in year 1 and year 2 using Kaplan–Meier estimates in Simonato et al[19] were 0.86 and 0. 80, respectively. When adjusting the costs to account for mortality, we assumed that deaths would happen at the end of month 6 in each year (i.e., the costs incurred in the first two quarters for these patients).

All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

BASELINE CHARACTERISTICS

The baseline characteristics of the 35 patients in our dataset are shown in Table A4. We identified 17, 12, and 6 patients who received TMViV in fiscal years 2018/19, 2019/20, and 2020/21, respectively. Of the 35 patients we identified, 21 (60%) were female and 14 (40%) male, and their mean age (± standard deviation) was 75 ± 15 years. Of the total, 77% (27/35) had at least one hospitalization within 1 year before TMViV.

Table A4: Baseline Characteristics, Patients Treated With TMViV Between Fiscal Years 2018/19 and 2020/21 in Ontario (N = 35)

Patient characteristic	Summary statistic[a]
Demographics	
Age, years	74.80 ± 15.05
Female	21 (60)
Neighbourhood income quintile	
1 (lowest)	8 (22.86)
2	9 (25.71)
3	6 (17.14)
4	8 (22.86)
5 (highest)	NR
Fiscal year of intervention	
2018/19	17 (48.57)
2019/20	12 (34.29)
2020/21 (incomplete fiscal year)	6 (17.14)
Most responsible diagnosis (ICD-10-CA code)	
I34, Nonrheumatic mitral (valve) insufficiency	21 (60)
T82, Complications of cardiac and vascular prosthetic devices, implants, and grafts	14 (40)
Hospitalization within 1 year before TMViV	
Yes	27 (77.14)
No	8 (22.86)
Medical comorbidities	
Chronic ischemic heart disease (ICD-10-CA: I25)	10 (28.57)
Primary hypertension (ICD-10-CA: I10)	16 (45.71)
Type 2 diabetes mellitus (ICD-10-CA: E11)	7 (20)
Atrial fibrillation and flutter (ICD-10-CA: I48)	9 (25.71)
Heart failure (ICD-10-CA: I50)	12 (34.29)
Dyslipidemia (ICD-10-CA: E78)	6 (17.14)

Abbreviations: ICD-10-CA, Classification of Diseases, 10th revision, Canadian version; SD, standard deviation; TMViV, transcatheter mitral valve-in-valve implantation; NR, not reported (fewer than 5 observations).
[a]Values are mean ± SD or n (%).

COSTS AND RESOURCE USE IN THREE PHASES

Phase-based costs and resource use are summarized in Table A5. The average inpatient costs in the procedure phase of TMViV were higher than those for transcatheter aortic valve implantation for patients with severe aortic stenosis ($29,982 vs. $26,048).[46] We also estimated that the average costs of hospitalization for TMViV (not including the physician fees) was $27,895 (95% CI $20,009 to $38,396).

Compared to the preprocedure phase, we found a decreasing trend in inpatient and ambulatory care visits and their associated costs in the postprocedure phase. Average costs in the postprocedure phase were approximately $5,000 (10 months of costs between 61 days and 1 year postprocedure), which was much lower than the costs at the preprocedure phase, which were approximately $16,000 for the 1 year before the procedure. The median (Q1, Q3) of the difference in monthly costs between the postprocedure and preprocedure phases was −$464 (−$1,261, −$79).

Table A5: Phase-Based Costs and Resource Use for Patients Treated With TMViV, Inpatient and Ambulatory Care[a]

Outcome	Preprocedure (1 year before procedure; n = 35)	Procedure (day of procedure to 60 days postprocedure; n = 35)	Postprocedure (61 days to 1 year postprocedure; n = 24)
Total costs, $			
Total costs, mean (95% CI)	16,102 (10,430–23,214)	30,508 (22,537–40,988)	4,974 (1,756–8,810)
Inpatient visit costs, mean (95% CI)	13,273 (7,799–20,117)	29,982 (22,020–40,575)	4,294 (1,273–7,965)
Ambulatory visit costs, mean (95% CI)	2,829 (2,269–3,430)	527 (86–1,270)	680 (375–1,009)
Inpatient care			
Patients with any visit, n (%)	27 (77.14)	10 (28.57)[a]	6 (25)
Number of hospitalizations, mean (95% CI)	1.46 (1.06–1.91)	0.29 (0.14–0.43)[b]	0.42 (0.13–0.75)
Cumulative RIW, mean (95% CI)	2.34 (1.37–3.54)	*Excluding index hospitalization* 0.37 (0.11–0.71) *Including index hospitalization* 5.28 (3.88 to 7.15)	0.76 (0.22–1.40)
Ambulatory care			
Patients with any visit, n (%)	35 (100)	9 (25.71)	15 (62.5)
Number of visits, mean (95% CI)	3.06 (2.46–3.71)	0.46 (0.17–0.77)	1.08 (0.63–1.54)
Cumulative RIW, mean (95% CI)	0.50 (0.40–0.60)	0.09 (0.02–0.22)	0.12 (0.07–0.18)

Abbreviations: CI, confidence interval; RIW, resource intensity weight; TMViV, transcatheter mitral valve-in-valve implantation.

[a]Some numbers may appear inexact due to rounding.

[b]Excluding hospitalization for the index treatment, 10 of 35 patients were rehospitalized within 60 days postprocedure.

SCENARIO ANALYSES

The results of our budget impact scenario analyses are summarized in Table 17 in the main text. This section details the cost parameters for scenarios 2, 3, and 4, which are also summarized in Table A6.

When we accounted for physician fees and drug costs (scenario 2), we found that costs increased to approximately $39,000 for TMViV in the procedure phase. When we limited our dataset to cases with the most responsible diagnosis of nonrheumatic mitral disease only (ICD-10-CA: I34; scenario 3), the costs across all three phases were slightly higher than those in our reference case. Finally, when we estimated health care resource costs using the Canadian national-level cost of a standard hospital stay (scenario 4), we found that our cost parameters were 12% higher than if we based our estimates on the provincial-level cost of a standard hospital stay, which we used in our reference case.

Table A6: Phase-Based Costs for Patients Treated With TMViV, Scenario Analyses[a]

Costs, $	Preprocedure (1 year before procedure)	Procedure (day of procedure to 60 days postprocedure)	Postprocedure (61 days to 1 year postprocedure)
Scenario 2: Accounting for physician fees and drug costs			
Total costs, mean (95% CI)	21,401 (13,862–30,852)	39,148 (28,919–52,595)	8,097 (2,859–14,341)
Scenario 3: Limiting the dataset to cases with the most responsible diagnosis of nonrheumatic mitral disease only (ICD-10-CA code I34) for TMViV (n = 21 for preprocedure and procedure; n = 17 for postprocedure)			
Total costs, mean (95% CI)	19,592 (11,118–30,344)	29,795 (20,018–44,954)	5,999 (1,610–11,047)
Inpatient cost, mean (95% CI)	16,816 (8,624–27,259)	29,628 (19,872–44,764)	5,288 (1,141–10,089)
Ambulatory visit cost, mean (95% CI)	2,776 (2,084–3,520)	166 (20–368)	711 (315–1,147)
Scenario 4: Using the national-level cost of a standard hospital stay			
Total costs, mean (95% CI)	18,093 (11,720–26,084)	34,280 (25,323–46,055)	5,589 (1,974–9,899)
Inpatient cost, mean (95% CI)	14,914 (8,763–22,605)	33,689 (24,742–45,592)	4,825 (1,430–8,950)
Ambulatory visit cost, mean (95% CI)	3,179 (2550–3,855)	592 (97–1,427)	764 (422–1,134)

Abbreviations: CI, confidence interval; CSHS, cost of a standard hospital stay; ICD-10-CA, International Statistical Classification of Disease, 10th revision, Canadian version; TMViV, transcatheter mitral valve-in-valve implantation.
Note: Excluding hospitalization for the index treatment, 10 of 35 people had hospitalizations within 60 days postprocedure.
[a]Some numbers may appear inexact due to rounding.

PREDICTED COSTS FOR STANDARD CARE OVER 2 YEARS AFTER THE INDEX DATE

We found a trend of increasing costs over time, which may have reflected disease progression in adults with degenerated mitral valve bioprostheses. After controlling for age, sex, and the main diagnosis in the prediction model, the mean cost increase was $470 per quarter. Our model predicted that without TMViV (i.e., standard care), costs for the first year after the index date would be $23,673, and costs for the second year would be $31,196. After adjusting for mortality, mean costs for standard care in years 1 and 2 would be $21,884 and $25,836, respectively.

Appendix 3: Letter of Information

LETTER OF INFORMATION

Ontario Health is conducting a review of **Transcatheter Heart Valve Implantation** for degenerated bioprostheses, a procedure to replace damaged heart valves. The purpose is to understand whether this procedure should be more broadly funded in Ontario.

An important part of this review involves speaking to patients (or family members) who have experience with this procedure or may be anticipating encountering this procedure in the future. Our goal is always to make sure the lived experience of individuals and families are considered in the funding recommendations for this procedure.

WHAT DO YOU NEED FROM PARTICIPANTS?

- ✓ 15-25 minutes of time for a phone or in-person interview to hear about their experiences
- ✓ Permission to audio- (not video-) record the interview

WHAT PARTICIPATION INVOLVES

If a participant agrees to share their experiences, they will be asked to have an interview with Ontario Health staff. The interview will likely last 15-25 minutes. It will be held in a private location or over the telephone. With consent, the interview will be audio-recorded. The interviewer will ask questions about perspectives of this surgical procedure, decision-making and more general thoughts about the potential use of the procedure and treatment in Ontario.

Participation is voluntary. Those who volunteer may decide not to participate, refuse to answer any questions or withdraw before the interview. Withdrawal will in no way affect the care received.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from the interview will be stored securely.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, participants can speak to our staff.

If you have any questions or are interested in participating, please contact Ontario Health staff:

Ontario Health

Appendix 4: Interview Guide

Interview for Valve-in-Valve procedure (TAVI HTA)

Intro
Explain OH purpose, HTA process, and purpose of interview

Lived- Experience
Symptoms and development of heart disease (or reason for valve procedure)?
Impact of symptoms on quality of life?
Medical journey to receiving diagnosis
Access to diagnosis and specialists – any barriers?

Treatments and Decision-Making for first surgery
Decision-making for initial valve surgery (if appropriate)?
Information about bioprosthetic valves (why choose)?
Decision-making surrounding different treatment options – what factors were important to you?

Valve-in-Valve Surgery
Pathway to viv surgery – was it planned in advance, was it based on symptoms?
Information about valve-in-valve surgery
- Well prepared?
- Concerns?
- What factors were most important to you?

Details of procedure?
Impact of procedure
- Functional outcomes – ability to do activities, QoL change?

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