Centre universitaire de santé McGill

McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre (MUHC)

Transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis

Update of Report No. 45

Report number: 70

DATE: August 31, 2013

Report available from http://www.mcgill.ca/tau

Report prepared for the Technology Assessment Unit (TAU)

of the McGill University Health Centre (MUHC)

by

Alison Sinclair, Xuanqian Xie, Maurice McGregor

Approved by the Committee of the TAU on May 21, 2013

TAU Committee

Andre Bonnici, Nandini Dendukuri, Sandra Dial,
Christian Janicki, Patricia Lefebvre, Brenda MacGibbon-Taylor,
Maurice McGregor, Gary Pekeles, Guylaine Potvin,
Judith Ritchie, Hugh Scott, Gary Stoopler

Suggested citation:

Sinclair A, Xie X, McGregor M. Transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis: Update of Report 45. Montreal (Canada): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2013 August 31 Report no. 70. 48 p.

Available from:

https://secureweb.mcgill.ca/tau/sites/mcgill.ca.tau/files/muhc_tau_2013_70_tavi.pdf

ACKNOWLEDGEMENTS

The expert assistance of the following individuals is gratefully acknowledged:

- Dr. B. E. de Varennes, Head, Division of Cardiac Surgery, MUHC
- Dr. N. Piazza, Cardiology Division, MUHC
- Dr. J. Martucci, Cardiology Division, MUHC
- Dr. D. Mylotte, Cardiology Division, MUHC
- D. Dubé, Patient Safety and Performance Department, MUHC
- E. Balok, Cardiac Surgery Department, MUHC
- M. Romero-Lopez, Cardiac Surgery Department, MUHC
- C. Berubé, Cardiology Division, MUHC

We are grateful to:

Dr. Marc Rhainds, Clinical professor in the Department of Preventive Medicine at Laval University and co-manager of medical and scientific activities at the Centre hospitalier universitaire de Québec, L'unité d'évaluation des technologies et des modes d'intervention en santé (CHUQ-ETMIS) for his assistance with the translation of our Executive Summary.

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When surgery is not precluded, valve replacement by TAVI or by surgery confer comparable increments of survival and functional improvement. TAVI is more expensive than surgery and is associated with paravalvular aortic regurgitation and a higher stroke rate.

From the perspective of the MUHC, the procedure cost for TAVI versus SAVR is $29,755 versus $17,395 respectively

It is recommended that for patients with severe symptomatic aortic stenosis, in whom surgery is considered not to be an option, valve replacement by the TAVI procedure should now be considered standard of care.

For patients for whom surgery is an available option, SAVR should normally be the chosen procedure.

LIST OF ABBREVIATIONS

AE	Adverse event
AVA	Aortic valve area
AVG	Aortic valve gradient
CADTH	Canadian Agency for Drugs and Technology in Health
CI	Confidence interval
CRD	Centre for Research and Dissemination
CUSM	Centre universitaire de santé McGill
DARE	Database of Abstracts of Reviews of Effects
ECR	Essai clinique randomisé
EMBASE	Excerpta Medica Database
ETSAD	Evaluation des technologies de santé pour l'aide à la décision
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FDA	Food and Drug Agency
HR	Hazard ratio
HTA	Heath technology assessment
ICER	Incremental cost-effectiveness ratio
INAHTA	International Network of Agencies for Health Technology Assessment
INESSS	L'Institut national d'excellence en santé et en services sociaux
IQR	Interquartile range
ITALY	CoreValve Italian Registry
IVAC	L'implantation valvulaire aortique par cathéter
LY	Life year
MUHC	McGill University Health Centre
NICE	National Institutes for Health and Clinical Excellence
NYHA	New York Heart Association
PARTNER	Placement of AoRTic TraNscathetER Valves (trial)
PVR	Paravalvular regurgitation
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
RR	Risk ratio
SAVR	Surgical aortic valve replacement
SOURCE	Edwards SAPIEN Aortic Bioprosthesis European Outcome (registry)
SURTAVI	Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (trial)
STS	Society for Thoracic Surgery
TA	Transapical

TAU	MUHC Technology Assessment Unit
TAVI	Transcatheter aortic valve implantation
TF	Transfemoral
TIA	Transient ischemic attack
UK TAVI	United Kingdom Transcatheter Aortic Valve Implantation (registry)

EXECUTIVE SUMMARY

Background

Transcatheter aortic valve implantation (TAVI) involves the insertion of a bioprosthetic aortic valve, either transarterially or transapically, to relieve symptomatic, severe native valve stenosis. Its original use was in patients with contraindications to surgery, but that use is now being extended to operable patients who are at high and intermediate surgical risk. This is an update of a previous TAU review (Report No 45, 2009) and a review of TAVI use at the MUHC.

Method

Literature search was carried out for publications in English and French published between January 1, 2009 and February 1, 2013 (see Appendix 1). Since TAVI has been extensively reviewed by others, we limited the review to health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, and observational studies reporting long-term results. We carried out a cost analysis from the MUHC perspective.

Results: Literature review

Randomized controlled trials (RCTs)

The only published RCT, the PARTNER trial of the Edwards SAPIEN valve, has been reported with up to two years follow-up. The trial consisted of two cohorts: PARTNER B recruited 358 patients who were considered inoperable for a variety of reasons, and PARTNER A recruited 699 patients considered operable but at high risk of death or disability from surgical valve replacement (SAVR).

Survival. In PARTNER B, *all-cause mortality* was significantly reduced in patients assigned to TAVI compared with those assigned to standard medical management with optional balloon aortic valvuloplasty: 30.7% versus 50.7% (hazard ratio 0.55, 95% CI 0.40 to 0.74) at one year, and 43.3% versus 68.0% at two years.

In PARTNER A, *all-cause mortality* was comparable (within the non-inferiority margin) between patients assigned to TAVI and those assigned to surgery: 24.2% versus 26.8% at one year (-2.6%, 95%CI -9.3%, 4.1%), and 33.9% versus 35.0% at two years.

Complications. The rate of *major stroke* at 30 days in PARTNER B was 5.0% for TAVI versus 1.1% for medical management, and in PARTNER A was 3.8% for TAVI versus 2.1% for SAVR.

The rate of *major vascular complications* at 30 days in PARTNER B was 11.0% for TAVI versus 3.2% for medical management, and in PARTNER A was 16.2% for TAVI versus 1.1% for SAVR.

Moderate/severe *paravalvular leak* was more common after TAVI than after surgery (12.2% for TAVI versus 0.9% for SAVR at 30 days). *Major bleeding* was more common in the surgical arm of PARTNER A (9.3% for TAVI versus 19.5% for surgery).

Systematic reviews/HTAs

We retrieved 15 HTAs in English and French published since 2009, most of which include PARTNER data up to one year follow-up.

There was a general consensus on the benefits of TAVI in patients considered unsuited for surgical valve replacement, for whom the alternative was medical management.

There was no consensus as to the benefits of TAVI in patients who were potential candidates for surgery. There is general agreement that survival and functional improvement are comparable following TAVI or open surgery. Authors of recent (2012) guidelines concluded TAVI was a reasonable alternative or could be considered for high risk patients. However several review bodies (including INESSS in Quebec, NICE in the UK and Health Quality Ontario) did not recommend TAVI rather than surgery because of increased risk of stroke, lack of long-term follow-up data, and economic considerations.

Other long-term results

Survival at two years or more has been reported for several large multicenter registries for both the Edwards SAPIEN valve and the Medtronics CoreValve. Mortality at two years in the registries ranged from 26.3% to 33%, compared with 33.9% in PARTNER A, and did not appear to depend on the valve implanted. By contrast, the two year mortality with medical management in the PARTNER B study was 68%. Valves appear to function normally for at least three years. In one five-year follow-up study involving 88 early patients the median survival was 3.4 years, and 3/88 patients had developed signs of prosthetic valve failure by end of follow-up.

Meta-analyses of adverse events indicate increased risk of stroke, particularly with the transarterial (predominately transfemoral) approach (4.2% versus 2.7% for the transapical approach), and increased risk of pacemaker implantation with use of the CoreValve compared to the Edwards SAPIEN (25.8% versus 6.5%).

Published economic evaluations

An economic analysis from the third party payer's perspective in Canada using data from the PARTNER A trial found procedure costs (physicians' fees included) of $46,337 and $32,946 for TAVI and surgery respectively. Another Canadian study, also based on PARTNER, found somewhat lower hospital procedure costs of TAVI, $38,904, including physicians fees.

Case Selection

Reviewers stress the importance of patient selection, which must take account of both severity of aortic stenosis and the overall risk of intervention. Several recommend case review and patient selection by a multidisciplinary team.

TAVI at the MUHC

Between December 2007 and February 28, 2013, 99 patients underwent TAVI at the MUHC, with either the Edwards SAPIEN or the Medtronics CoreValve. Three patients were converted to surgical valve replacement (3%), and six (6.1%) suffered a periprocedural stroke. The thirty day mortality was 6.1%, and after a median follow-up of 307 days, 28/99 (28.6%) had died. Kaplan-Meier one-year mortality was 20%. These results are comparable to the outcomes reported in the literature.

Cost analysis

The estimated procedure costs were $29,755 for TAVI and $17,395 for SAVR (incremental cost $12,360). Calculated one-year health costs were $34,708 for TAVI and $22,175 for SAVR (incremental cost $12,534). Due to the large uncertainties of cost for inoperable patients, it is difficult to estimate the incremental costs of TAVI versus medical management. The estimates of healthcare were obtained using a probabilistic model with cost inputs based on MUHC data and data from the Ontario Case Costing Initiative, and efficacy inputs based on PARTNER.

CONCLUSIONS

- **Symptomatic severe aortic stenosis carries a grave prognosis, with survival rates of approximately 50%, 35% and 20% at one, two, and three years with medical treatment, including valvuloplasty.**
- ***In inoperable patients* there is evidence of benefit from aortic valve replacement by TAVI, with marked functional improvement and survival rates of the order of 95%, 69.3%, and 56.7% at 30 days and one and two years respectively, based on data from the PARTNER B trial. There is wide consensus that for such patients TAVI is appropriate treatment.**
- ***In high-risk operable patients* it is unclear whether TAVI has an advantage over surgical valve replacement. Survival and complication rates are comparable, with the exception that TAVI resulted in more paravalvular regurgitation (moderate to severe in 12.2% versus 0.9% at 30 days [PARTNER A], with apparently little progression for up to 3 years) and stroke (4.7% versus 2.4% at 30 days, and 6.0% versus 3.1% at one year, respectively).**
- ***Costs.* From the perspective of the MUHC, the procedure cost for TAVI versus SAVR is $29,755 versus $17,395 respectively (a difference of $12,360). Comparison of costs in TAVI versus medical management in inoperable patients is less certain, since it is difficult to estimate the cost of medical management precisely.**

RECOMMENDATIONS

- **For patients with reduced life expectancy due to severe symptomatic aortic stenosis, in whom surgery is considered not to be an option, if age and comorbidity are such that a continuing life of adequate quality can be anticipated, valve replacement by the TAVI procedure should now be considered standard of care.**
- **For patients for whom surgery is an available option, SAVR should normally be the chosen procedure.**
- **The practice of sharing responsibility for patient selection by a multidisciplinary team, of recording that this has been done, and of recording all relevant clinical material in a registry, as recommended by INESSS, should continue.**

SOMMAIRE

Contexte

L'implantation valvulaire aortique par cathéter (IVAC) implique l'insertion, transartérielle ou transapicale, d'une bioprothèse de la valve aortique, pour traiter la sténose aortique symptomatique sévère. Cette procédure était originalement réservée aux patients qui avaient des contrindications chirurgicales, mais est maintenant étendue aux patients opérables qui sont à risque chirurgical élevé et intermédiaire. Ce document est une mise à jour d'un précédent rapport d'évaluation de l'Unité d'évaluation des technologies du Centre universitaire de santé McGill (CUSM) (Rapport # 45, 2009) qui intègre également une revue de l'utilisation de l'IVAC au CUSM.

Méthodologie

Une recherche documentaire a été menée pour identifier des documents publiés en anglais et en français entre le 1er janvier 2009 et le 1er février 2013. Ce sujet ayant déjà été traité de manière exhaustive par d'autres auteurs, la présente recherche se limite aux rapports d'évaluation des technologies, aux revues systématiques/méta-analyses, aux essais cliniques randomisés (ECR) ainsi qu'aux études observationnelles qui rapportent des résultats à long terme. Une analyse des coûts a été réalisée en tenant compte de la réalité du CUSM.

Résultats. Revue de la littérature

Essai clinique randomisé (ECR)

Le seul ECR identifié est l'étude PARTNER portant sur l'utilisation de la valve Edwards SAPIEN chez les patients suivis jusqu'à deux ans. L'essai était composé de deux cohortes. Au total, 358 patients qui étaient inopérables pour une variété de raisons ont été recrutés dans la cohorte B alors que 699 patients opérables mais présentant un risque élevé de mortalité ou une incapacité à avoir un remplacement valvulaire aortique par chirurgie (RVAC) ont été inclus dans la cohorte A .

Survie: Dans la cohorte B, la mortalité toutes causes a été significativement réduite chez les patients assignés à l'IVAC comparativement à ceux soumis au traitement médical standard avec option de valvuloplastie aortique par ballonnet: 30,7% comparativement à 50,7% (hazard ratio : 0,55; IC à 95% : 0,40 à 0,74) à un an, et 43,3% comparativement à 68,0% à deux ans, respectivement.

Dans la cohorte A, la mortalité toutes causes était comparable (à l'intérieur de la marge de non-infériorité) entre les patients affectés à l'IVAC et à la chirurgie: 24,2% comparativement à 26,8% à un an (différence d'incidence : -2.6%; IC à 95% : -9,3%, 4,1%) et 33,9% comparativement à 35,0% à deux ans, respectivement.

Complications: La fréquence d'accidents vasculaires cérébraux à 30 jours dans la cohorte B était de 5,0% chez les patients assignés à l'IVAC comparativement à 1,1% chez ceux sous traitement médical standard. Dans la cohorte A, ce taux était de 3,8% pour les patients assignés à l'IVAC comparativement à 2,1% pour ceux ayant eu un RVAC.

Le taux de complications vasculaires majeures à 30 jours était pour la cohorte B, de 11,0% pour les patients assignés au groupe IVAC comparativement à 3,2% pour ceux sous traitement médical alors que pour la cohorte A, le taux s'élevait à 16,2% pour ceux traités par IVAC comparativement à 1,1% pour ceux assignés au groupe RVAC.

Les fuites paravalvulaires modérées ou graves à 30 jours étaient plus fréquentes après l'IVAC (12,2%) qu'après une chirurgie (0,9%). Les hémorragies majeures étaient plus fréquentes dans le groupe RVAC de la cohorte A soit 19,5% comparativement à 9,3% pour le groupe IVAC.

Revues systématiques/Rapports d'évaluation des technologies

Au total, 15 rapports d'évaluation des technologies publiés en anglais et en français ont été identifiés, dont la plupart incluent les résultats à un an de suivi de l'étude PARTNER.

Dans l'ensemble, il se dégage un consensus général sur les avantages de l'IVAC chez les patients considérés inaptes à subir une chirurgie pour un remplacement valvulaire aortique et pour qui l'alternative est la prise en charge médicale.

Il n'y a pas de consensus sur les avantages de l'IVAC chez les patients qui sont des candidats potentiels à la chirurgie. Il est généralement admis que la survie et l'amélioration fonctionnelle sont comparables après l'IVAC ou une chirurgie ouverte. Les auteurs de récentes lignes directrices (2012) ont conclu que l'IVAC est une alternative raisonnable à la chirurgie qui pourrait être considérée pour les patients à risque élevé. Toutefois, plusieurs organismes en évaluation des technologies et des modes d'intervention en santé (incluant INESSS au Québec, NICE au Royaume-Uni et Health Quality Ontario) ne recommandent pas l'IVAC en remplacement de la chirurgie en raison du risque accru d'accidents vasculaires cérébraux, de l'absence de donnée de suivi à long terme et de considérations économiques.

Autres résultats à long terme

La survie à deux ans ou plus a été rapportée par plusieurs grands registres multicentriques à la fois pour la valve Edwards SAPIEN et la CoreValve de Medtronic. Dans ces registres, la mortalité à deux ans variait de 26,3% à 33%, comparativement à 33,9% dans la cohorte A de l'étude PARTNER, et ne semblait pas dépendre du type de valve implantée. En comparaison, le taux de mortalité à deux ans pour les patients sous prise en charge médicale dans la cohorte B de l'étude PARTNER était de 68%. Les valves aortiques semblent fonctionner normalement pendant au moins trois ans. Dans une étude impliquant 88 patients

suivis pendant cinq ans, la survie médiane était de 3,4 ans et 3 d'entre eux ont développé des signes de défaillance de la prothèse valvulaire en fin de suivi.

Les méta-analyses d'événements indésirables indiquent un risque accru d'accidents vasculaires cérébraux, en particulier avec l'approche transartérielle principalement celle transfémorale (4,2%) comparativement à l'approche transapicale (2,7%), de même qu'un risque accru d'implantation d'un stimulateur cardiaque avec l'utilisation de la CoreValve comparativement à la valve Edwards SAPIEN (25,8% vs 6%, respectivement).

Évaluations économiques publiées

Une analyse économique canadienne basée selon une perspective du tiers payeur a été réalisée en utilisant les données de la cohorte A de l'étude PARTNER. Les coûts de procédure incluant les honoraires des médecins, ont été estimés à partir des résultats d'une étude et s'élève à 46 337 $ pour l'IVAC et à 32 946 $ pour la chirurgie. Une autre étude canadienne, également basée sur les résultats de l'étude PARTNER, a estimé des coûts de procédure IVAC (incluant les honoraires des médecins) légèrement plus faibles, soit de 38 904 $.

Sélection des cas

Les auteurs des publications identifiées soulignent l'importance de la sélection des patients qui doit tenir compte à la fois de la gravité de la sténose aortique et du risque global de l'intervention. Plusieurs d'entre eux recommandent que l'évaluation des cas et la sélection des patients soient réalisées par une équipe multidisciplinaire.

IVAC au CUSM

Entre décembre 2007 et le 28 février 2013, 99 cas d'IVAC ont été pratiqués chez des patients du CUSM, soit avec la valve Edwards SAPIEN ou la Medtronic CoreValve. La procédure a été convertie en remplacement valvulaire aortique par chirurgie chez trois patients (3%) et six patients (6,1%) ont développé un accident vasculaire cérébral périopératoire. La mortalité à 30 jours était de 6,1%. Après un suivi médian de 307 jours, 28 des 99 patients (28,6%) étaient décédés. L'estimation de la mortalité à un an basée sur la méthode Kaplan-Meier était de 20%. Ces résultats sont comparables à ceux rapportés dans la littérature.

L'analyse des coûts

Les frais de procédure s'élevaient à 29 755 $ pour l'IVAC et à 17 395 $ pour le RVAC (coût différentiel de 12 360 $). Les coûts de santé calculés pour une période d'un an étaient de 34 708 $ pour l'IVAC et de 22 175 $ pour le RVAC (coût différentiel de 12 534 $). L'estimation des coûts marginaux de l'IVAC comparativement à ceux d'un traitement médical est difficile à établir en raison de la grande incertitude sur les coûts reliés aux patients inopérables. Les données du

CUSM, de l'Ontario Case Costing Initiative de même que celles de l'étude PARTNER ont été utilisées pour procéder à l'estimation des coûts selon un modèle probabiliste.

CONCLUSIONS

- **La sténose aortique symptomatique sévère sous traitement médical (incluant la valvuloplastie) est associée à un mauvais pronostic avec des taux de survie à un, deux et trois ans d'environ 50%, 35% et 20%, respectivement.**
- **Selon les résultats de la cohorte B de l'étude PARTNER, chez les patients inopérables, il y aurait un effet bénéfique associé au remplacement de la valve aortique par IVAC chez les patients qui ne sont pas des candidats à la chirurgie, avec une amélioration marquée du fonctionnement et des taux de survie à 30 jours, un an et deux ans de l'ordre de 95%, 69,3% et 56,7%, respectivement. Il existe un large consensus pour ces patients que l'IVAC est un traitement acceptable.**
- **Chez les patients à risque élevé qui sont des candidats à la chirurgie, il est difficile de déterminer dans quelle mesure l'IVAC a un avantage sur le remplacement valvulaire aortique par chirurgie. Les taux de survie et de complications sont comparables, à l'exception de certains résultats suggérant que l'IVAC entraînerait davantage de régurgitations paravalvulaires modérées à sévères (12,2% vs 0,9% des patients à 30 jours [cohorte A de l'étude PARTNER], et peu de progression jusqu'à trois ans) et d'accidents cérébrovasculaires (4,7% vs 2,4% à 30 jours et 6,0% vs 3,1% à un an, respectivement).**
- **Du point de vue du CUSM, les coûts reliés à la procédure d'IVAC s'élèvent à 29 755 $ comparativement à 17 395 $ pour le RVAC (différence de 12 360 $). La comparaison des coûts liés à l'IVAC à ceux des patients inopérable sous traitement médical ne peut être réalisée en raison de la difficulté à estimer précisément les coûts de la prise en charge médicale.**

RECOMMANDATIONS

- **Pour les patients qui ont une espérance de vie réduite en raison d'une sténose aortique symptomatique sévère et pour lesquels la chirurgie n'est pas une option à considérer, le remplacement de la valve par la procédure d'IVAC devrait être considéré comme la norme de soins si l'âge et les comorbidités du patient permettent d'envisager que ce dernier puisse survivre avec une qualité de vie adéquate.**
- **Pour les patients pour lesquels la chirurgie est une option disponible, le RVAC devrait normalement être la procédure favorisée.**

- **Tel que recommandé par l'INESSS, le partage de la responsabilité de la sélection des patients par une équipe multidisciplinaire, l'enregistrement de ces données de même que l'archivage dans un registre de tous les documents cliniques pertinents est une pratique en cours qui devraient être maintenue.**

Transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis

Update of report No. 45

1. BACKGROUND

Calcific aortic stenosis is a disease of the elderly, characterised by progressive narrowing of the aortic valve. Once symptoms (angina, heart failure, blackouts) develop, prognosis becomes extremely limited. The only treatment that will prolong life is replacement of the defective valve by an artificial valve, a procedure that is traditionally carried out at open surgery under cardiac arrest. However, since 2002, procedures have been developed by which a prosthetic valve can be installed by catheterisation, via the femoral or subclavian arteries or the cardiac apex. These procedures are called transcatheter aortic valve implantation or TAVI.

A 2009 review carried out by the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) concluded that[1]:

- This is an effective technology that should continue to be funded by the MUHC.
- Since this is a relatively new procedure, and one in which both the selection of patients and its execution are crucial for success, the Cardiovascular Division should maintain a registry, including follow-up, of all cases.
- The registry should be examined by the MUHC in approximately one year at which time the decision to continue funding should be reviewed.

The present report, carried out at the request of Mr. Gary Stoopler, Administrative Director, MUHC, consists of an update of the current literature on the TAVI procedure, and a review of the MUHC experience since 2009.

At present, two TAVI devices (valve and implantation assembly) have been granted a Class IV license in Canada, the Edwards SAPIEN valve on June 22, 2011[2], and the Medtronics CoreValve on August 1, 2012[3]. In both cases, the approved indication is for severe, symptomatic aortic stenosis in a patient considered inoperable (having ≥50% risk of death or irreversible morbidity from surgical aortic valve replacement).

2. OBJECTIVE(S)

- To update Report No 35 and reestimate the effectiveness, safety and costs of TAVI for aortic valve stenosis.
- To review the use and outcomes of TAVI at the MUHC.

3. METHODS

3.1. Literature search

The search for technology assessments described in the 2009 TAU report was repeated with additional terms that have subsequently come into use, and restricted to 2009 and later (Appendix 1). We searched health technology assessment databases INAHTA, CRD, Cochrane, NICE, INESSS and ETSAD, for health technology assessments. We also searched PubMed and EMBASE (through Ovid), for systematic reviews, meta-analyses and RCTs, using the supplied filters to identify these specific study types, and for long-term follow-ups of registry studies using identifying text words. To retrieve economic studies we used the terms cost(s) and economic(s). We limited our search to English and French language reports.

One author (AS) conducted the search, and two authors screened and reviewed papers (AS, MM). The search was last updated to January 23, 2013.

3.2. Cost analysis

3.2.1. Cost analysis of TAVI versus surgical valve therapy

We compared the one year health care costs for the two treatments. We estimated costs from the perspective of the MUHC, focusing on the costs for personnel and medical devices. The estimates of the average healthcare resource uses (OR time, ICU stay, CCU stay etc.) were mainly based on 853 surgical valve procedures and 62 TAVI procedures conducted between 2008 and 2012 at MUHC, for which complete data could be obtained. We used Microsoft Excel 2007 in analyses and Visual Basic for Applications (VBA) in Excel for the Monte Carlo Simulation. All costs were expressed in Canadian Dollars (CAD$) 2013.

See Appendix 3 for details.

4. RESULTS

4.1. Results of literature search

4.1.1. Randomized controlled trials

One-year[4,5] and two-year results[6,7] have been published for the Placement of AoRTic TraNscathetER Valves (PARTNER) trial. Two separate cohorts were recruited. In PARTNER B, implantation of an Edwards SAPIEN valve by TAVI was compared with standard medical management (which in 83.8% of patients included balloon valvuloplasty) in 358 patients considered ineligible for surgery[4,6]. In PARTNER A, TAVI was compared with surgical aortic valve replacement (SAVR) in 699 patients considered operable but at high risk of death or major morbidity with surgery[5,7]. In

the latter cohort, patients were stratified prior to randomization according to route of implantation, transfemoral (preferred) or transapical. As PARTNER B finished recruitment before PARTNER A, recruitment of inoperable patients continued as a Continued Access Study. Results for the 90 patients recruited were presented to the FDA[8] and referred to by Neyt and Van Brabant[9], but have not yet been published. Available results have also been published for the prematurely-terminated STACCATO trial, which compared placement of an Edwards SAPIEN valve via the cardiac apex with surgical aortic valve replacement in elderly patients[10].

4.1.2. Health technology assessments and clinical practice guidelines

We found 15 health technology assessments in either English or French that had been released since 2009[11-25], ranging from rapid reviews to systematic reviews. The protocol for an in-progress Cochrane review has also been published[26].

Within Quebec, INESSS published a systematic review and meta-analysis of the evidence retrieved as of January 2011[11] (subsequently published as Boothroyd et al, 2012[27]), following a 2010 expert review by a working group of the Réseau québécois de cardiologie tertiaire (RQCT)[28].

Within Canada, CADTH published three successive rapid reviews of various aspects of TAVI as the evidence accumulated in December 2009[12], September 2011[13], and January 2013 (draft released for public review)[14], and an environment scan of current patterns of use and upcoming developments in February 2013[15]. Health Quality Ontario published a full health technology assessment and economic analysis[16] (the latter was also released as a peer reviewed publication, Doyle et al, 2012[29]).

Outside Canada, the UK National Institute for Health and Clinical Excellence (NICE) published an interventional procedural guidance in March 2012[17], based on an overview completed in April 2011[18]. The French Haute Autorité de Santé (HAS, 2011) updated its 2008 report with a systematic review[19] and the Belgian Health Care Knowledge Centre (BKE) updated its 2008 assessment in 2011 with a review of RCT and registry results and an economic assessment[20] (followed by a peer-reviewed publication, Neyt et al, 2012[30]). Agencies in Scotland[21,22] and Australia[23] published reports or technical briefings. The Netherlands College voor zorgverzekeringen (Health Care Insurance Board) released an English-language assessment[31].

The US Agency for Healthcare Research and Quality (AHRQ) released a 2010 technical briefing on percutaneous heart valve replacement[24], including aortic valve replacement, which was used as the basis for a published systematic review (Coeytaux et al, 2010)[32]. This, like the previous TAU TAVI report, preceded the publication of any RCT data. Additional US publications included a systematic review from the California Technology Assessment Forum[25] and a policy statement from Blue Cross Blue Shield Kansas City[33].

The American College of Cardiology Foundation, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons released a joint expert consensus document[34], and the Canadian Cardiovascular Society produced a position statement, both in 2012[35]. The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) assessed TAVI as part of their "Guidelines on the management of vascular heart disease (version 2012)"[36].

In our assessment we primarily used those most relevant to our local context (INESSS, CADTH, HQO, and North American position statements).

4.1.3. Long-term follow-up results

Two-year survival data for patients undergoing TAVI have been reported for the multi-centre SOURCE registry (a post-marketing registry for the Edwards SAPIEN valve)[37,38] and the UK TAVI registry (an independently-funded UK national registry collecting data for all valves)[39]. Survival up to three years has been reported for the CoreValve Italian registry (ITALY)[40], and up to four years for the Canadian TAVI Multicentre experience registry (CANADA)[41,42].

4.2. TAVI versus medical management in patients considered inoperable

4.2.1. Randomized controlled trial

PARTNER B. The *Placement of AoRTic TraNscathetER Valves* (PARTNER) trial, was a multicentre randomized controlled trial of TAVI (using the Edwards SAPIEN valve) compared with surgical aortic valve replacement of native stenosed aortic valves in high risk patients (PARTNER A), and with standard medical management in patients considered inoperable (PARTNER B). Entrants to PARTNER B had to have a post-operative risk of death or serious irreversible morbidity of ≥50% within 30 days of conventional aortic valve surgery or be otherwise considered inoperable because of anatomic abnormalities, prior surgery, or other thoracic disease. In addition, patients in PARTNER B had to be eligible for valve implantation by the transfemoral route.

Between May 2007 and March 2009, 179 patients were randomized to TAVI and 179 to standard care. Randomized groups were well balanced at baseline, although some commentators[9] have expressed concern that there was a slight excess of patients with anatomical contraindications to surgery assigned to TAVI and a slight excess of patients with significant comorbidities assigned to standard care, which could potentially favour TAVI. The mean STS scores were 11.2±5.8 and 12.1±6.1 for TAVI and standard care patients, respectively.

PARTNER Cohort B showed significantly lower one-year all-cause mortality in patients assigned to the Edwards SAPIEN valve group via TAVI (30.7% at one year,

by Kaplan-Meier analysis), compared with those who assigned to standard medical management with optional balloon valvuloplasty (50.7%; hazard ratio 0.55, 95% CI 0.40 to 0.74)[4]. Two year follow-up results were consistent, with a rate of death of 43.3% in the TAVI group versus 68.0% with standard therapy[6]. In a small non-randomized subset of control arm patients who were eligible for TAVI in the second year, those who underwent TAVI had lower mortality than those who did not (10% versus 21%). Censoring these patients at the time of crossover did not change the results. At two years, TAVI halved the rate of repeat hospitalization (35% versus 72.5% for standard care), and considerably increased the median number of days alive and out of hospital (699 days [IQR 201, 720]) versus 355 days [IQR 116, 712]. At two years, 83.1% of survivors assigned to TAVI were in New York Heart Association (NYHA) Class I or II versus 42.5% of those managed with standard care.

As might be expected, there was a peri-procedural mortality associated with TAVI, with a 30-day death rate (from the time of randomization) of 5.0% versus 2.8% for medical management (which included valvuloplasty in 83.8% of patients). TAVI was associated with an increased rate of stroke at both early and late time-points: for TAVI versus medical management, stroke at 30 days was 6.7% versus 1.7%, and at 2 years was 13.8% versus 5.5%. This was due to both an early excess of ischemic stroke (6.7% versus 1.7%) and a later excess of haemorrhagic stroke (2.2% versus 0.6%). Nevertheless, the composite risk of death and stroke was significantly lower in TAVI compared with standard care (46.1% versus 68.0%).

Once recruitment was complete for PARTNER B inoperable patients were recruited into the PARTNER Continued Access Study until recruitment for PARTNER A was complete. As reported to the FDA, the one-year mortality for these patients was 34.3% (n=41) for TAVI versus 21.6% for those assigned to standard care (n=49)[8]. These results have not been published in full, so it is difficult to assess the implications.

4.2.2. Health technology assessments and guidelines

There is general agreement amongst reviewers that for patients with severe, symptomatic aortic stenosis who are judged not to be candidates for surgery, the use of TAVI resulted in significantly better survival with superior quality of life, compared with medical management[11-23,25,36,43]. The INESSS reviewers concluded that TAVI "can be considered for patients with symptoms attributable to severe aortic stenosis and for whom valve surgery is contra-indicated or judged to be excessively risky"[43]. The 2012 North American expert consensus document on transcatheter aortic valve replacement concludes that “TAVR [TAVI] is recommended in patients with prohibitive surgical risk”[34]. The ECS/EACTS guideline for the management of valvular heart disease indicates that “TAVI is indicated in patients with severe symptomatic aortic stenosis who are not suitable for AVR as assessed by a ‘heart team’ and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities” (Level B

recommendation)[36]. The reports also reiterate the importance of careful patient selection for TAVI and involvement of a multidisciplinary team involving both cardiologists and cardiac surgeons.

Although these conclusions were almost entirely based on the results of one study, the PARTNER B RCT, they gain credibility because the results of this trial are consistent with the existing evidence, namely that in cases with symptomatic severe calcific aortic stenosis life expectancy is severely limited and, in the absence of life-limiting comorbidity can be returned to near-normal by surgical replacement of the aortic valve by a prosthesis[44]. If this is accepted, it only remains to be shown that the artificial valve can be equally well installed by catheter, and that it will continue to function satisfactorily thereafter. The evidence for this is described in the next section.

4.3. TAVI versus surgical aortic valve replacement in patients considered eligible for surgery

4.3.1. Randomized controlled trials

PARTNER A. For patients eligible for surgery but at high risk, the PARTNER trial compared TAVI (using the Edwards SAPIEN valve) with SAVR (Cohort A)[5,7]. Entrants to PARTNER A had to be at high risk of operative complications, or have a 30-day risk of death from surgery ≥15% (a decision based on expert opinion guided by an STS≥10%)[45]. Participants were stratified before randomization by their suitability for implantation via the iliofemoral vasculature ("transfemoral" or TF, the preferred route) or access via the left ventricular apex ("transapical" or TA). The sample size calculation for PARTNER A was powered for comparison of TAVI versus surgery for all patients and for those undergoing implantation via the transfemoral route of access, but not for undergoing implantation by the transapical route.

A total of 699 participants were randomized, 348 to TAVI, 351 to SAVR. Within the TAVI group, 244 participants were assessed as eligible for transfemoral implantation, 104 as eligible for transapical implantation.

Randomized groups were well balanced at baseline, with an overall mean score on STS of 11.8% indicating overall high operative risk. The transapical access stratum had a higher proportion of patients with previous CABG, cerebrovascular disease, and peripheral vascular disease, which is unsurprising since they were selected by the quality of vascular access. Forty-two of the 699 patients did not undergo the assigned procedure, 4 in the TAVI group and 38 in the surgery group, most commonly as a result of withdrawal or decision not to undergo surgery.

Mortality. The one year rate of death was 24.2% in all patients assigned to receive TAVI versus 26.8% in patients assigned to surgery, a difference of -2.6 (95% CI -9.3,

4.1), which was within the noninferiority margin (upper limit of the one-sided 95% CI, 3.0 percentage points; non-inferiority margin, 7.5%)[5]. At two years, the rate of death for any cause was not significantly different between patients assigned to TAVI, 33.9% (95% CI 28.9, 39.0) and those assigned to surgery, 35.0% (95% CI 29.8, 40.2)[7]. Among survivors at two years follow-up, the mean NYHA class was similar (TAVI 1.72, SAVR 1.70) and the majority of patients in both groups were in NYHA Class I or II (TAVI 83.9% versus SAVR 85.2%).

For patients eligible for transfemoral implantation, the one-year rate of death was 22.2% for those assigned to TAVI (n=244) and 26.4% (n=248) for those assigned to surgery, and the two-year rate of death was 30.9% for TAVI versus 34.6% for surgery. The one-year comparison was adequately powered, and fell within the noninferiority limit. For patients eligible for apical implantation, the one-year rate of death was 29.0% for those assigned to TAVI (n=104) and 27% (n=103) for those assigned to TAVI, and the two-year rate of death was 41.1% for TAVI and 35.7% for SAVR. There was no prespecified sample or effect size for this comparison.

Stroke. While there was a higher rate of stroke in the TAVI group in the first 30 days following surgery (TAVI 4.7% versus SAVR 2.4%), in subsequent months there were more strokes in the surgery group, with the result that at 36 months follow-up there was no significant difference between the two groups (HR 1.22, 95%CI 0.67, 2.23).

A separate post-hoc analysis (Miller et al, 2012)[46] of all neurological adverse events (34 strokes and 15 TIAs in 47 patients) out to two years follow-up identified a period of increased hazard in the first week associated with TAVI, and constant late hazard determined by patient- and disease-related factors (functional impairment by NYHA Class and prior stroke).

Other complications. *Major vascular complications* were more common in the TAVI group at one year (11.3% versus 3.8%), but there were virtually no further such events in the subsequent year. There were no significant differences at one or two years in the frequency of *endocarditis, renal failure*, or the use of a new *pacemaker*. No patient in either group experienced *valve deterioration* requiring replacement and at two-year follow-up there was no significant difference in the rates of *re-hospitalization* (TAVI 24.7% versus SAVR 21.7%).

STACCATO. The STACCATO trial (Nielsen et al, 2012[10]) was a randomized controlled trial of TAVI with the Edwards SAPIEN valve via the transapical route versus surgical valve replacement in patients aged ≥75 years who were candidates for surgery. Planned recruitment was 200 patients, but the study was prematurely terminated after the inclusion of 70 patients on the advice of the data safety monitoring board due to the unexpectedly high number of patients meeting the composite endpoint in the TAVI group. Five patients in the TAVI group met the composite endpoint of 30-day all cause mortality (one patient died while waiting for the procedure and one died after surgical intervention when the prosthesis blocked the left coronary artery), major stroke (two patients), or renal failure requiring dialysis

(one patient), versus one patient with major stroke in the surgery group. In addition, one of the TAVI patients with stroke subsequently died, and one TAVI patient died after SAVR for severe PVL.

4.3.2. Health technology assessments

The role of TAVI versus surgical aortic valve replacement in patients in whom surgery is judged to be an option is less certain. In the PARTNER A trial, comparing TAVI with surgery, the difference in one-year mortality was within the pre-specified non-inferiority margin[5]. However, the increased risk of certain adverse events, especially stroke, the short follow-up in these patients with longer potential life expectancy, and the cost impact of TAVI led several institutions, including NICE[17,18], Health Quality Ontario[16], and BKE[20] to not recommend the use of TAVI in patients who were candidates for surgery.

In the CADTH rapid response released for review January 2013[14] the objective was to compare long-term (>2 year) TAVI outcomes with those of surgery or medical management. Besides the two-year follow-up of the PARTNER trial[6,7] and the post-hoc meta-analysis of neurological adverse events described above[46], they identified two additional comparative studies:

Jilaihawi et al, 2012[47], carried out a Bayesian meta-analysis of complications in 5024 TAVI procedures (64.1% with the Edwards SAPIEN valve) and 3512 surgical aortic valve replacements. This analysis included uncontrolled observational studies published up to September 2010, plus the one-year results of the PARTNER B study. There were no significant differences in mortality between TAVI and SAVR: 30-day mortality was 8.5% versus 8.8% (p=0.31), one year mortality was 22.8% versus 18.4% (p=0.65) and two-year mortality was 26.5% versus 23.3% (p=0.54, derived from a small number of studies). Other outcomes were (TAVI versus surgery): stroke to 30 days, 2.6% versus 2.4%, new permanent pacemaker, 12.1% versus 5.9%, and new dialysis, 4.1% versus 2.4%. The use of a CoreValve was associated with higher rates of new pacemaker implantation (24.5% versus 5.9% for ES implanted by the transfemoral approach).

Wenaweser et al, 2011[48], carried out a prospective comparison of post-operative mortality rates involving 257 and 107 patients treated by TAVI and SAVR respectively. Patients were allocated to treatment on clinical criteria, therefore those allocated to TAVI had a higher STS score (6,4% versus 4.8% for SAVR), more cardiovascular comorbidity and previous procedures, and a higher mean NYHA Class. At 30 months, outcomes were comparable: for TAVI versus surgery, all cause mortality was 22.6% versus 22.4%, major stroke was 4.3% versus 4.7%, and a composite endpoint of death, major stroke or MI was 25.7% versus 24.3%. They concluded that clinical outcomes “seem similar” when patients are carefully selected.

The CADTH reviewers concluded that compared with surgical management in carefully selected patients, TAVI produced similar clinical and hemodynamic outcomes, but that vascular and neurological adverse events were more frequent.

The 2012 ECS/EACTS guideline for the management of valvular heart disease[36], the Canadian Cardiovascular Society position statement[35], and the ACCF/AATS/SCAI/STS expert consensus document[34] indicated that TAVI was a reasonable alternative or could be considered for patients with severe symptomatic aortic stenosis who were at high surgical risk, whose life-expectancy with treatment was liable to exceed 1-2 years, whose quality of life was expected to improve, and about whom a multidisciplinary heart team could reach a consensus.

4.4. Observational studies with long term follow-up

As previously indicated, we sought cohort and registry reports that included long-term outcomes. These are summarized in Table 3 and Figure 1.

Two-year mortality was 32.5% in SOURCE, 26.3% in UK TAVI, 30.0% in ITALY, and 33% in the Canadian TAVI Multicentre experience, compared with 33.9% observed in PARTNER A. **Three and four year mortality** in the Canadian registry were 49% and 57% respectively[41], and one registry site has recently reported 35% survival (65% mortality) in their cohort at five years[49] (see below). Survival was not dependent on the type of valve (UK TAVI). Survival in patients who had received a valve by the transfemoral route was better than those who had received a valve by the transapical or other route (PARTNER A, SOURCE, UK TAVI), which is thought to be a reflection of generalized atherosclerosis and the associated risk.

In general the age and severity of patients in registries are fairly comparable to the patients recruited for the PARTNER cohorts. Mean Logistic EuroSCORE was 26.2% in SOURCE[37], 18.5% (median) in UK TAVI[39], and 24% in ITALY compared to 29.3% and 26.4% for PARTNER A and B, respectively. For ITALY and the Canadian registry, mean STS was 11.4%[40] and 9.8%[37], compared with 11.8% in PARTNER A. However, comparison across registries is limited by the use of different scoring systems, and scoring systems themselves do not necessarily capture all the potential risk factors or the reasons for inoperability.

Outcomes to 30 months (2.5 years) were compared for TAVI, SAVR, and medical management in all patients diagnosed with aortic stenosis at a single-centre registry in Switzerland, as described above[48]. Prior to adjustment for baseline characteristics, mortality at 2.5 years was 22.6% for TAVI, 22.4% for SAVR, and 61.5% for medical management; with adjustment for baseline differences, the hazard ratio for death for TAVI versus medical management was 0.38 (95% CI 0.25, 0.58) and for SAVR versus medical management was 0.51 (95%CI 0.3, 0.87).

Outcomes for TAVI to 5 years were reported by Toggweiler et al, 2013[49] for a cohort of inoperable patients treated in Vancouver between January 2005 and March 2007, using the Edwards SAPIENS and the previous generation Cribier-Edwards

valves. In this early cohort, procedural failure and short-term mortality was relatively high. In 88 patients who had undergone a successful procedure and survived beyond 30 days, the median survival was 3.4 years (95%CI 2.5, 4.4), and Kaplan-Meier mortality rates were 26% at 2 years, 47% at 3 years, 58% at 4 years and 65% at 5 years. Their mean age was 83 years and mean STS score was 9.0. During follow-up of the survivors, mean AVA slowly declined (0.06 cm^2/year) and AVG increased (0.27 mmHg/year). Up to four years follow-up, there were no signs of prosthetic valve failure, but at five years, three patients showed moderate regurgitation and/or stenosis. None required reintervention.

4.5. Patient selection

Reviewers of the TAVI data have emphasized the importance of patient selection, which must take account of several variables.

Severity of aortic stenosis. Intervention before the quality and quantity of life are severely limited involves unnecessary surgical risk and is to be avoided. Indicators of severity are fairly well defined[27], although their clinical application clearly requires clinical judgement.

Severity of comorbidities. The risk of death and/or severe complications in the first 30 days is substantially influenced by the severity of comorbidities, and degree of risk can be estimated by the STS (The Society of Thoracic Surgeons Predicted Risk of Mortality) score and the logistic EuroSCORE. The former is reported to show moderately better ability to predict early mortality in the context of TAVI[34,35]. The value of this score in predicting 30 day mortality is confirmed by the stratified analysis of the two-year PARTNER B[6] data, which showed that survival after TAVI versus medical management was related to STS score, as follows: Patients with an STS of ≥15% had HR of death 0.77 (95% CI 0.46, 1.28, n=90), those with an STS between 5% and 14.9%, HR 0.58 (95% CI 0.41, 0.81, n=227), and those with an STS <5%, HR 0.37 (95% CI 0.13, 1.01, n=40).

Prediction of long-term outcome. The INESSS reviewers recommend that TAVI should only be considered for patients for whom “there is reasonable probability that quality of life (related to functional capacity, autonomy and activities of daily living) would improve significantly as a result of the intervention, and be sustained for at least 1 year”. (See Boothroyd et al, 2012[27]. Appendix 2)

4.6. Meta-analyses of adverse events

Major concerns that have emerged are increased risk of stroke, need for new pacemaker implantation post TAVI, and adverse effects of severe paravalvular leak.

Stroke. In a meta-analysis of 53 studies including a total of 10,037 patients undergoing TAVI for aortic stenosis published between January 2004 and November 2011[50], Eggbrecht et al, 2012, found an overall incidence of 1.5% for procedural

stroke, 3.3% for strokes at 30 days (2.9% for strokes described as major), and 5.2% for strokes at 1 year (reported only in a few studies). Study definitions of neurological events were used, without adjudication. Stroke was higher in patients who had undergone implantation by the transarterial (predominately transfemoral) route than the transapical route (4.2 versus 2.7), and with a CoreValve (narrower gage) rather than an Edwards SAPIEN valve. Peri-interventional stroke was associated with a 3.5-fold increase of death (patients with stroke 25.5% versus 6.9% in patients without). The mean age of patients in the meta-analysis was 81.5 years, their mean EuroSCORE was 24.8%, 57.2% received an Edwards SAPIEN valve and 43.6% received a CoreValve.

Pacemaker implantation. Erkapic et al, 2012[51], reported on the incidence and risks of pacemaker implantation after TAVI in a meta-analysis of 32 studies with 5,258 patients (2,887 with an Edwards SAPIEN valve, and 2,371 with a CoreValve). Their search was restricted to PubMed and covered up to April 2011. Overall, 15% of patients required a pacemaker (6.5% of ES patients and 25.8% of CV patients). In their analysis, pre-existing right bundle branch block was a significant predictor of complete AV block and subsequent pacemaker implantation.

Paravalvular regurgitation Generaux et al, 2013[52], reviewed the literature linking PVL to outcomes in the form of a narrative synthesis (following a systematic review of all adverse events). Both method of measurement and timing of measurement varied across studies. Post-procedural PVL was slightly more frequent with the self-expanding CoreValve (9% to 22%, depending upon source) than with the balloon-expanded Edwards valves (6% to 13.9%). Moderate/severe PVL was infrequent and the degree of PVL was generally stable over the available follow-up time. However, in some studies, significant residual aortic regurgitation appeared to be an independent predictor of failure to respond to therapy at six months and of death over the short and long term[52]. Furthermore, the 2-year follow-up data of the PARTNER A trial suggested an association between PVL and late mortality, HR 2.11, 95% CI 1.43, 3.10[7]. The association held even for mild PVL. Patient-prosthesis mismatch is a significant predictor of PVL.

4.7. Ongoing research

A search of ClinicalTrials.gov retrieved entries for four in-progress RCTs evaluating TAVI versus surgery, or comparing the performance of different valves. These are summarized in Appendix 2.

4.8. Published cost analyses

We retrieved 9 published cost analyses comparing the cost of TAVI with surgery or medical management within the Canadian[29,53], UK or European[30,54-56], and US systems[57-59]. Two US-based reports used economic data prospectively collected in the PARTNER trial[58,59], while the majority of the others used Markov decision-analytic modelling with inputs derived from the PARTNER trial. One study used

prospectively collected clinical data with propensity score matching to compare costs for TAVI and surgery for patients at intermediate surgical risk[55]. We discuss those we consider most relevant to the Quebec experience below.

Doble et al. 2012[29] published a Canadian economic analysis analysed from the third party payer's perspective. The authors constructed a Markov decision analytic model to compare the cost-effectiveness of TAVI with standard medical management for inoperable patients, and with SAVR for operable patients over a 20 year time horizon. The key clinical parameters of their model were based on the PARTNER trial, with costs for transapical and transfemoral approaches aggregated. As the authors only had one-year data available for PARTNER, they used the age-specific Canadian life table to estimate the mortality rates for years two to 20 for all patients, on the rationale that these would reflect comorbidities in the population[60]. The procedure cost, hospitalization cost, cost of medications, cost of complications and associated cost of long-term health consequences, etc, were included in their cost estimate.

The 20-year costs (including physician fees) for inoperable patients receiving TAVI and standard medical management were $88,991 and $57,963, respectively, and for operable patients, of TAVI and SAVR were $85,755 and $74,602, respectively.

Given the advanced age of the typical patient with degenerative aortic stenosis, a time horizon of 20 years, though standard methodology, was not realistic. In addition, use of the Canadian life table to estimate the mortality rates beyond 1 year is liable to overestimate survival, as the risks of death for inoperable patients treated with TAVI appear to be higher than those in the corresponding age and sex specific population. Median 30-day survival in the longest TAVI 5-year follow-up cohort was 3.4 years (Toggweiler et al, 2013[49]), compared with a 7.14 years for male and 8.62 year for female life expectancy for people of a comparable mean age in the Canadian population as a whole[61]. We calculated a rate ratio for death in the Toggweiler cohort versus the Canadian population in the 2nd year of 1.54 (95%CI 0.77, 3.07), the 3rd year of 3.87 (95%CI 2.44, 6.14), the 4th year of 2.54 (95%CI 1.37, 4.72) and the 5th year of 1.74 (95%CI 0.78, 3.87). Finally, with the passage of time, a variable portion of the long-term costs for patients living at a distance from the MUHC would be assumed by other health facilities closer to the patients' domicile.

Nevertheless, this unsponsored, contemporary, Canadian study provides procedure and first year costs that are likely comparable to those that would be experienced at the MUHC. Procedure costs, plus pharmacy, were $46,337 and $32,946 for TAVI and SAVR, respectively. (Note that the cost of the valve and catheter is now approximately $15,600 lower than when these estimates were made).

Hancock-Howard et al, 2013[53] used the results of PARTNER B, Canadian (Ontario) and French resource costs (where Canadian were not available) to estimate cost-effectiveness using a deterministic decision analytic model. Costs were calculated for a 3-year horizon, using PARTNER data for years one and two, and extrapolation

for the third year. For TAVI, the procedure cost for an uncomplicated case was calculated as $38,904, including physicians' fees. The total cost of TAVI over three years was $58,357 versus $42,670 for medical management. (Again, medical management included balloon aortic valvuloplasty).

Murphy et al 2013[54] used the results of PARTNER B and contemporary UK costs to estimate the procedure costs of TAVI to be £20,755. Using a Markov model, they assessed the lifetime costs of TAVI versus medical care in inoperable patients to be £28,061 versus £12,176.

Reynolds et al, 2012[58,59], based their economic analyses on the cost, quality of life, and survival data collected for the PARTNER A and PARTNER B studies, from a US societal perspective. For operable patients (PARTNER A)[58], the cost of the index admission, excluding physicians costs, for *transfemoral* TAVI (234 patients) versus surgical valve placement (221 patients) was almost identical $68,358 versus $68,309 (US), respectively. However, the costs for *transapical* TAVI were higher, with an average cost for TA-TAVI (101 patients) versus SAVR (99 patients) of $85,277 versus $72,903, respectively. For inoperable patients (PARTNER B)[59], all of whom underwent a transfemoral procedure, the mean cost of the index admission for TAVI patients was $73,562 (without physicians' fees).

Reynolds et al calculated one-year costs for TF-TAVI of $96,743 versus $97,992 for SAVR, for TA-TAVI of $109,405 versus $99,499 and for inoperable patients, $106,076 versus $53,921 for medical managment. In doing so, they made a number of assumptions that were potentially to the advantage of TAVI. They estimated survival beyond study follow-up time using a parametric survival model that was fitted independently for each group. For TAVI, the best fit was obtained by conditioning survival at 3 months, which led to a longer survival estimate. In addition, their method of projecting survival for subjects who survived beyond follow-up could potentially overestimate survival, again to the advantage of TAVI. Lifetime costs were projected from the last six months observed for each patient, which in the medical management patients were more likely to be the terminal six months, leading to higher cost estimates.

5. TAVI AT THE MUHC

5.1. MUHC TAVI experience to date

From the inception of the MUHC TAVI program in December 2007 to February 28, 2012, 99 patients underwent TAVI at the MUHC, including the 12 originally included in the 2009 MUHC report[1]. Currently two valves are in use, the Edwards SAPIEN and the Medtronics CoreValve. The median age at procedure was 83 years (range 58 to 96 years), and 61% were in NYHA Class III or IV. The median STS surgical risk score was 6.1% (range 1.1% to 25.3%).

The majority of patients received a valve via the transfemoral route (58, 59.2%), followed by the transapical route (34 patients, 34.7%). Three patients were converted to surgical valve replacement (3%), and six (6.1%) suffered a stroke within 30 days. Of the first 90 patients, 10 (11.8%) had a major vascular adverse event. Eleven of the full cohort (11.1%) needed pacemaker implantation (for one the status was unknown). Median length of stay following TAVI was 8 days (interquartile range 5, 13 days).

The median follow-up for the cohort was 307 days (range 0 to 1822 days). Six patients (6.1%) died in the first 30 days after the procedure, and 28 (28.6%) of patients died during overall follow-up. Five of the patients who died were in the first half of the cohort. Kaplan-Meier one-year survival was 80% (n=43), and two-year survival 64% (n=24).

MUHC outcomes are broadly comparable to those from PARTNER (Table 1).

Table 1 Comparison of MUHC TAVI experience with PARTNER

	MUHC n=99	PARTNER A n=348	PARTNER B n=179
Age, mean (years)	82.1	83.6	83.1
Male (%)	52.3	57.8	45.8
STS (%) mean±SD*	7.1±4.4	11.8±3.3	11.2±5.8
30-day mortality (%)	6.1	3.4	5.0
1-year mortality (%)	20	24.3	30.7
2-year mortality (%)	36	33.9	43.3
Stroke, 30-day (%)	6.1	4.7	6.7
Vascular repair (%)	11.8	11.0	16.8

*Note that STS values are not constant over time and comparison between these values should not be made without caution

5.2. Cost analysis

5.2.1. Cost analysis of TAVI versus SAVR in operable patients

We calculated a procedure cost of $29,755 for TAVI and of $17,395 for SAVR, (incremental cost $12,360) and a total cost to the MUHC in the first year of $34,708 for TAVI and of $22,175 for SAVR (Table 2). See Appendix 3 for methods and inputs. The incremental cost of TAVI in the first year was $12,534. Univariate sensitivity analyses that varied the inputs by 25% produced incremental costs of $7,034 to $18,034, with the widest range produced by the variation in the device cost of TAVI. The probabilistic sensitivity analysis produced a mean incremental cost in the first year of $12,529±1,218.

Table 2 Results of cost analysis of TAVI versus surgical valve therapy (per patient)

	TAVI	SAVR	Incremental cost
Cost of procedure and hospitalization	7,755	13,395	--
Cost of valve, catheter, etc.	22,000	4,000	--
Cost of complications in 1 year	4,953	4,779	--
Total healthcare cost in 1 year	34,708	22,175	12,534

All costs were expressed in Canadian dollars in 2013.

6. DISCUSSION

In considering the strength of the evidence underlying the following conclusions several issues should be recognised.

- First, although it is the consensus of numerous reviews and HTAs that TAVI is superior to medical management and that there is no significant difference between the outcomes of TAVI and surgical management, the preponderance of the evidence on which these conclusions are based rests on one RCT, the PARTNER trial, for the Edwards SAPIEN valve. Evidence based on the consensus of multiple reviewers is no stronger than that of the original source article on which the reviewers depend.
- It should also be noted that many of the PARTNER reports and economic analyses were supported by the manufacturer of the valve, some being co-authored by company employees.
- Although in practice the majority of aortic valves are implanted via the transfemoral route, alternate, more invasive routes are also used. RCT evidence for these is limited: The comparison of transapical TAVI and surgery in PARTNER A was not powered, there was no transapical TAVI arm in the PARTNER B trial and the STACCATO trial of transapical implantation was discontinued prematurely due to an excess of adverse events in the TAVI arm. None of the other routes have been studied under RCT conditions.
- It should also be noted that, at present there is no RCT evidence comparing the Medtronics CoreValve valve with either medical management or surgery. Such evidence will be forthcoming with the results of the ongoing SURTAVI trial[62]. Registry data suggests comparable results for most outcomes for the two valve types, with the exception of pacemaker implantation, which is approximately five-fold more frequent for the CoreValve prosthesis. Pacemaker implantation is not a perfect surrogate for the development of heart-block, as it is dependent on practice.
- Practice is moving ahead of evidence, in that there is already an increasing tendency to use TAVI in lower surgical risk patients in the expectation of better outcomes than with surgery. In their single centre German study, Lange et al,

2012[63] found a movement towards lower surgical-risk patients over time. Both the PARTNER-II[64] and the SURTAVI[62] trials, which are ongoing, compare TAVI (with the next generation Edwards SAPIEN XT valve and with the Medtronics CoreValve respectively) with SAVR in intermediate risk patients.

- Although there is ample long-term follow-up data supporting the safety of valve replacement by surgery, such evidence is only available for two and at most three years following TAVI. For younger patients with an otherwise good life expectancy, use of the procedure in advance of the evidence should not be undertaken lightly.
- In the cost estimates, we used crude data, ignoring potential differences in the patients' baselines. Indications for TAVI and surgical valve therapy are different at MUHC and usually TAVI is reserved for more severe patients, so it is difficult to get two groups of patients with similar baseline characteristics using the local data. This would slightly favour surgical valve therapy in estimating procedure and hospitalization costs.

7. CONCLUSIONS

- **Symptomatic severe aortic stenosis carries a grave prognosis, with survival rates of approximately 50%, 35% and 20% at one, two, and three years with medical treatment, including valvuloplasty.**
- ***In inoperable patients* in whom risk is too high for surgery, there is evidence of benefit from aortic valve replacement by TAVI, with marked functional improvement and survival rates of the order of 95%, 69.3%, and 56.7% at 30 days and one and two years respectively, based on data from the PARTNER B trial. There is wide consensus that for such patients TAVI is appropriate treatment.**
- ***In high-risk operable patients* it is unclear whether TAVI has an advantage over surgical valve replacement. Survival and complication rates are comparable, with the exception that TAVI resulted in more paravalvular regurgitation (moderate to severe in 12.2% versus 0.9% at 30 days [PARTNER A], with apparently little progression for up to 3 years) and stroke (4.7% versus 2.4% at 30 days, and 6.0% versus 3.1% at one year, respectively).**
- ***Costs.* From the perspective of the MUHC, the procedure cost for TAVI versus SAVR is $29,755 versus $17,395 respectively (a difference of $12,360). Comparison of costs in TAVI versus medical management in inoperable patients is less certain, since it is difficult to estimate the cost of medical management precisely.**

8. RECOMMENDATIONS

- **For patients with reduced life expectancy due to severe symptomatic aortic stenosis, in whom surgery is considered not to be an option, if age and comorbidity are such that a continuing life of adequate quality can be anticipated, valve replacement by the TAVI procedure should now be considered standard of care.**
- **For patients for whom surgery is an available option, SAVR should normally be the chosen procedure.**
- **The practice of sharing responsibility for patient selection by a multidisciplinary team, of recording that this has been done, and of recording all relevant clinical material in a registry, as recommended by INESSS, should continue.**

TABLES AND FIGURES

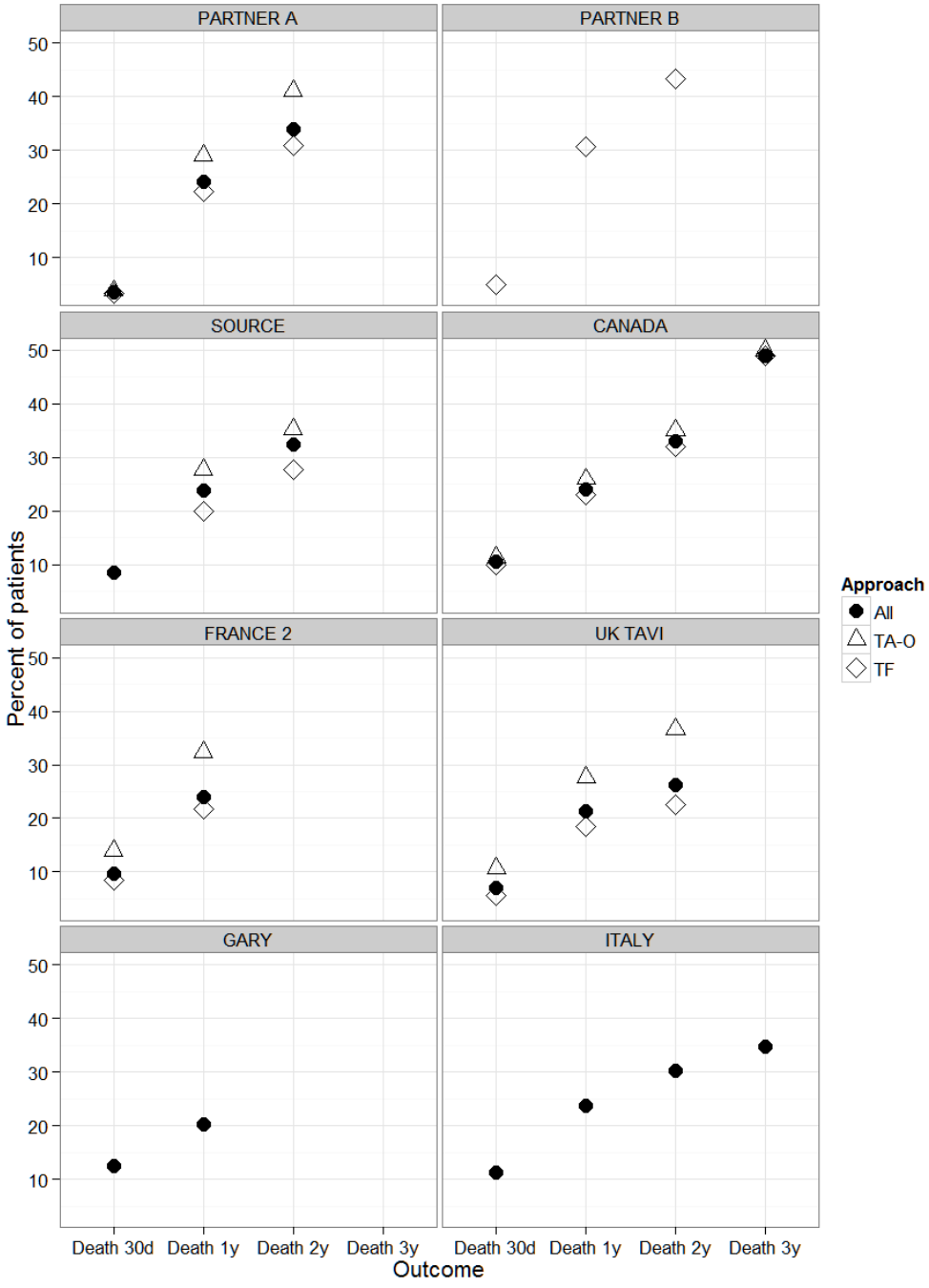
Table 3 Long-term follow-up in TAVI registries (with PARTNER trial for comparison)

	UK TAVI[39]	SOURCE[37,38]	Canadian[41,42]	Italian[17]	PARTNER A[5,7] TAVI group	PARTNER B[4,6] TAVI group
Enrollment	All TAVI in UK, 2007-2009.	Multicentre, post-marketing. November 2007 on.	All TAVI at 6 Canadian centres. January 2005 - June 2009.	All Italian TAVI. June 2007 - August 2008.	High-risk surgical patients meeting RCT criteria.	Patients deemed inoperable meeting RCT criteria.
N patients (procedures)	870 (877)	2307	339 (345)	181	348	179
Age (years), Male %	81.9, 52.4		81, 44.8	80.1, 44.2	83.6, 57.8	83.1, 45.8
NYHA III/IV %	77		90.9	68.5	94.3	92.2
Euroscore, mean %	18.5 (median)	26.2		24	29.3	26.4
STS, mean %			9.8	11.4	11.8	11.2
Valve implanted %	CV 52.3. ES 47.6	ES 100	CE 16.5, ES 81.7	CV 100	ES 100	ES 100
Mortality All Cause %						
30 day	7.1	8.5	10.6	11.2	3.4	5.0
1 year	21.4	23.9	24	23.6	24.3	30.7
2 years	26.3	32.5	33	30.3	33.9	43.3
3 years			49	34.8		
4 Years			57			
Stroke %						
Early	In-hospital, 4.1		30-day, 2.3		30-day, 4.7	6.7
All follow-up		2.5	6.8		2-year, 7.7	2-year, 13.8

	UK TAVI[39]	SOURCE[37,38]	Canadian[41,42]	Italian[17]	PARTNER A[5,7] TAVI group	PARTNER B[4,6] TAVI group
Major stroke %						
Early				30-day, 2.8	30-day, 3.8	30-day, 5.0
All follow-up				3-year, 3.9	-	-
Myocardial infarction %						
Early	30-day, 1.3		30-day, 1.2	30-day, 5.1	30-day, 0	30-day, 0
All follow-up			Fatal, 3.9	3-year, 5.6	2-year, 0	2-year, 1.6
AR moderate/severe %	30-day, 13.6	5.4		3-year, 10.1	6.9	2-year, 10
Major vascular complications %	30-day, 6.3	12.8	30-day, 13.3	30-day, 3.3	30-day, 11.0	30-day, 30.7
Major bleeding %						
Early					30-day, 9.3	30-day, 16.8
All follow-up				3-year, 10.7	2-year, 19.0	2-year, 28.9
Pacemaker %	30-day, 16.3	7.0	30-day, 4.9	30-day, 12.1	30-day, 3.8	30-day, 3.4

CAD, coronary artery disease; CE, Cribier-Edwards valve, previous generation to Edwards SAPIEN; COPD, chronic obstructive pulmonary disease; CV, Medtronics CoreValve; ED, any Edwards Valve (Edwards-Cribier or Edwards SAPIEN); ES, Edwards SAPIEN; MI myocardial infarction.

Figure 1 Mortality rates at follow-up in multicentre TAVI registries (with PARTNER trial for comparison)



All, valve implanted by any route; TA-O, valve implanted by transapical or other route; TF, valve implanted by transfemoral route.

CANADA, Multicentre Canadian Experience study (Edwards-Cribier/Edwards SAPIEN valves)[41,42]; FRANCE 2, French Aortic National CoreValve and Edwards[65]; GARY, German Transcatheter Aortic Valve Interventions – Registry[66]; ITALY, CoreValve Italian Registry[40]; PARTNER A, PARTNER trial Cohort A; PARTNER B, PARTNER trial Cohort B; SOURCE, Edwards SAPIEN Aortic Bioprosthesis European Outcome[37,38]; UK TAVI, United Kingdom Transcatheter Aortic Valve Implantation[39].

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APPENDICES

Appendix 1 Search terms

The systematic search in the 2009 TAU report[1] used the terms 'transcatheter aortic valve" AND "implantation OR replacement OR insertion" NOT "valvuloplasty" in a search of HTA databases [INAHTA, CRD, Cochrane, NICE, AETMIS, and CADTH], MEDLINE [including: In-Process & Other Non-Indexed Citations] and EMBASE (both via Ovid Online). Other inclusion criteria included: publication since 2002 in peer-reviewed journals, valve placement via the trans-femoral and trans-apical routes, and case series of ten cases or more.

We repeated the search with additional relevant terms, and restricted to 2009 and later.

> transcatheter OR percutaneous OR transcutaneous OR transfemoral OR transapical OR transubclavian OR transaortic OR transcarotid
>
> AND
>
> "aortic valve" OR "aorta valve"
>
> AND
>
> implantation OR transplantation OR replacement OR insertion

In addition, we added the abbreviation "TAVI", and specific terms for the two valves in use at MUHC, "Edwards SAPIEN" and "CoreValve".

The HTA search included INAHTA, CRD, Cochrane, NICE, AETMIS, and CADTH, with the addition of ETSAD (France). In searching for HTAs we also searched the equivalent terms in French ("remplacement percutané de valves aortiques", "implantation percutanée de valves aortiques").

The same terms in English were used to search PubMed and EMBASE (through Ovid), for systematic reviews, meta-analyses and RCTs, using the supplied filters to identify these specific study types. In EMBASE, we mapped terms to the keyword, "transcatheter aortic valve implantation", which was added to the dictionary in June 2011. Again, searches were restricted to 2009 and later.

A general search of PubMed and EMBASE to retrieve registry and single-centre studies with >2-year follow-up used the above terms for TAVI with text words "registry", "mid-term", "long-term", "2-year/two-year" (and variants), "3-year/three-year" (and variants) and "4-year/four-year".

Appendix 2 RCTs comparing valves, planned and in progress

The PARTNER-II (ClinicalTrials.gov NCT01314313)[64] trial of the next generation Edwards SAPIEN XT valve is modelled after PARTNER. Cohort A includes patients at intermediate surgical risk (STS≥4%, in contrast to PARTNER-I, where STS≥10%). They will be randomized to undergo implantation of the next generation Edwards SAPIEN XT valve (experimental arm), or surgical valve replacement with a bioprosthetic valve, stratified by transfemoral or transapical route of access. PARTNER-II Cohort B includes patients considered inoperable, ie, at ≥50% probability of death or serious, irreversible morbidity, similar to those recruited for PARTNER-I. They will be randomized to receive Edwards SAPIEN XT (experimental) or a Edwards SAPIEN valve (control), such as was used in the PARTNER-I trial, by the transfemoral route only. The primary outcomes are time to death, major stroke, or repeat hospitalization, and a non-heirarchical composite of these three events, assessed at 2 years for Cohort A and 1 year for Cohort B. The planned total enrolment is up to 2000 in cohort A, up to 500 in cohort B. In addition, there are three nested registries of up to 100 patients each who received the Edwards SAPIEN XT valve, including patients undergoing valve-in-valve implantation for structural deterioration of a prior surgical bioprosthetic valve. The estimated date for final data collection for the primary endpoint is March 2015, and study completion May 2018.

In the SURTAVI trial (ClinicalTrials.gov NCT01586910)[62], participants with severe, symptomatic aortic stenosis and STS between 4 and 10% inclusive (intermediate risk) will be randomized to receive a Medtronic CoreValve or to undergo surgical valve replacement. Primary outcomes are death from any cause or disabling stroke assessed at 2 years, with follow-up for 5 years. The planned total enrolment is 2500 patients, with a study start date of March 2012. No end dates were given.

In the NOTION trial (ClinicalTrials.gov NCT01057173)[67,68], an investigator-initiated trial at two Scandinavian centres, patients aged 70 years or over with symptomatic severe aortic stenosis who are potential candidates for TAVI or surgery will be randomized to receive a Medtronic CoreValve via TAVI or undergo surgical valve replacement. Primary outcome is a composite of death from any cause, myocardial infarction, or stroke at one year. The planned total enrolment is 280 patients, and enrolment began December 2009. Date of primary completion is December 2013.

In the CHOICE trial (ClinicalTrials.gov NCT01645202)[69], a single-centre trial in Germany, patients aged 75 years or over with symptomatic severe AS who are at high risk (EuroSCORE≥20% and/or STS≥10%) or inoperable will be randomized to receive an Edwards SAPIEN XT valve or a Medtronic CoreValve. Primary outcome is device success, while secondary outcomes include one year survival. The planned total enrolment is 240 patients, with a start date of March 2012 and primary data completion April 2014.

In addition, a multicentre UK trial of TAVI versus surgery is in the planning stages (http://www.uktavi.org, Accessed February 21, 2013).

Appendix 3 Methods for cost analysis

Cost analysis of TAVI versus surgical valve therapy

PARTNER A compared TAVI with surgical aortic valve replacement in patients considered at high risk for surgery (for results, see Section 4.3.1). Although TAVI was associated with a slightly lower 30-day mortality rate, the 1-year survival of TAVI was comparable with that for surgical valve therapy[5]. For simplicity, we compared the 1 year health care costs for the two treatments, disregarding the small potential health benefit of TAVI. We estimated costs from the perspective of the MUHC, focusing on the costs for personnel and medical devices. This estimate included the costs of purchasing the Edwards SAPIEN or Medtronics CoreValve valve and catheter or surgical prosthetic valve, operating room (OR), nurse, anaesthesia technician, radiology technician, ICU stay, CCU stay, hospitalization and treatment for complications. We excluded the costs for medications, tests and physician fees.

The estimates of the average healthcare resource uses (OR time, ICU stay, CCU stay etc.) were mainly based on the 853 surgical valve procedures and 62 TAVI procedures conducted between 2008 and 2012 at MUHC (see Table 4). The risks of complications of both therapies were assumed to be same as those in PARTER A[5] (see Table 5), and the corresponding costs for the treatments were obtained from the Ontario Case Costing Initiative (OCCI) reported by Doble et al, 2012[29] (see Section 4.8 for a description of the published study). We performed a univariate sensitivity analysis by changing ±25% of the mean values to identify the key parameters impacting the incremental cost. We also performed probabilistic sensitivity analysis using second-order Monte Carlo Simulation to explore the distribution of incremental costs. We used Microsoft Excel 2007 in analyses and Visual Basic for Applications (VBA) in Excel for the Monte Carlo Simulation. All costs were expressed in Canadian Dollars (CAD$) 2013.

Table 4 Healthcare resource use and unit price for TAVI and surgical valve therapy. Data source: MUHC*

	Mean	Distribution†
Resource use for the surgical valve therapy		
Anesthesia technician (hours)	4.62	Normal (4.62, 0.08)
Operating room (hours)	4.68	Normal (4.68, 0.08)
Cardiology unit, including CCU stay (days)	0.76	Gamma (36, 0.02)
ICU stay (days)	3.63	Gamma (169, 0.02)
Additional length of stay in hospital (days)	11.72	Normal (11.72, 0.59)
Resource use for the TAVI therapy		
Anesthesia technician (hours)	3	Fixed
Nursing (2 nurses) (hours)	6	Fixed
Radiology technician (hours)	3	Fixed
Cardiology unit, including CCU stay (days)	10.79	Gamma (47, 0.23)
ICU stay (days)	0.27	Gamma (1, 0.24)
Additional Length of stay in hospital (days)	1.77	Gamma (7, 0.25)
Price of valve, catheter, cannula and other disposable ($ CAD 2013)		
The devices for surgical valve therapy in total	4,000	Fixed
The devices for TAVI therapy in total	22,000	Fixed
Unit price of healthcare resource ($ CAD 2013)		
Operating room per hour	884	Fixed
ICU stay per day	1,288	Fixed
Hospitalization (Surgical Nursing) per day	338	Fixed
Cardiology unit, including CCU per day	593	Fixed
Technician fees of anesthesia per hours	37	Fixed
Nurse per hour	33	Fixed
Radiology technician per hour	30	Fixed

* Source: Length of stay by nursing unit for TAVI and SAVR supplied by D. Dubé. Cost of devices and staffing for TAVI supplied by C. Berubé. Operating room time for SAVR supplied by E. Balok.

† Normal distribution (mean, standard deviation); Gamma distribution (alpha, beta).

Table 5 Risks of complications and costs for complications

	Mean	Distribution (α, β)	Reference
Risk of complication up to 1 year: TAVI			
Myocardial Infarction	0.0029	Beta (1, 347)	Smith, 2011[5]
Major stroke	0.0489	Beta (17, 331)	Smith, 2011
Major bleeding	0.1408	Beta (49, 299)	Smith, 2011
Major vascular complication	0.1121	Beta (39, 309)	Smith, 2011
Acute kidney injury	0.0862	Beta (30, 318)	Smith, 2011
Prosthetic valve endocarditis	0.0057	Beta (2, 346)	Smith, 2011
New pacemaker (Prosthetic valve-associated complications)	0.0546	Beta (19, 329)	Smith, 2011
New-onset atrial fibrillation	0.1207	Beta (42, 306)	Smith, 2011
Risk of complication up to 1 year: SAVR			
Myocardial Infarction	0.0057	Beta (2, 349)	Smith, 2011
Major stroke	0.0228	Beta (8, 343)	Smith, 2011
Major bleeding	0.2422	Beta (85, 266)	Smith, 2011
Major vascular complication	0.0342	Beta (12, 339)	Smith, 2011
Acute kidney injury	0.0798	Beta (28, 323)	Smith, 2011
Prosthetic valve endocarditis	0.0085	Beta (3, 348)	Smith, 2011
New pacemaker (Prosthetic valve-associated complications)	0.0456	Beta (16, 335)	Smith, 2011
New-onset atrial fibrillation	0.1709	Beta (60, 291)	Smith, 2011
Cost of complication ($CAD in 2010)*			
Myocardial Infarction	10,949	Gamma (91, 120)	Doble, 2012[29]
Myocardial Infarction in the first year	3,116	Gamma (177, 18)	Doble, 2012
Major stroke (temporary disability)	1,669	Gamma (127, 13)	Doble, 2012
Major stroke (temporary disability) in first year	10,925	Gamma (16, 683)	Doble, 2012
Major bleeding	3,040	Gamma (26, 116)	Doble, 2012
Major vascular complication	5,342	Gamma (46, 116)	Doble, 2012
Acute kidney injury	15,780	Gamma (16, 986)	Doble, 2012
Prosthetic valve endocarditis	19,913	Gamma (8, 2388)	Doble, 2012
New pacemaker (Prosthetic valve-associated complications)	13,039	Gamma (369, 35)	Doble, 2012
New-onset atrial fibrillation	7,773	Gamma (76, 102)	Doble, 2012
Paravalvular leaks	25,302	Gamma (19, 1364)	Doble, 2012

*: Cost estimates were derived from the database of Ontario Case Costing Initiative (http://www.occp.com/).