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

Surgical aortic valve replacement with the ATS Enable® sutureless aortic valve for aortic stenosis

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by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

PRINCIPAL MESSAGES

Implantation of an aortic valve that does not need to be sutured in place is reported to reduce the time and invasiveness associated with standard surgical aortic valve replacement, potentially decreasing surgical risk and morbidity in selected patients.

The available evidence is limited. It suggests that the procedure is reasonably safe and produces good clinical outcomes up to the limit of follow-up (one year). Optimal patient selection, side effect profile (particularly relative to the more established alternatives), and long-term efficacy (beyond ~1 year) remain to be defined.

Use of SuAVR via mini-sternotomy instead of SAVR via standard sternotomy will have a budget impact to the MUHC of $3,750 per case. Offset savings may result in some increased efficiency

It is concluded that there is insufficient evidence to support the general introduction of the sutureless aortic valve, but there is sufficient evidence of safety and short term efficacy to justify temporary, conditional approval with maintenance of a case registry.

LIST OF ABBREVIATIONS

ACC	Aortic cross clamping
AE	Adverse event
ATS 3f	ATS 3f Aortic Bioprosthesis Model 1000
ATS Enable	ATS Enable Sutureless Bioprosthesis Model 6000
AVR	Aortic valve replacement
CCU	Coronary care unit
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CRD	Centre for Research and Dissemination
CUSM	Centre universitaire de santé McGill
DARE	Database of Abstracts of Reviews of Effects
EMBASE	Excerpta Medica Database
EuroSCORE	European System for Cardiac Operative Risk Evaluation
ICU	Intensive Care Unit
INAHTA	International Network of Agencies for Health Technology Assessment
MUHC	McGill University Health Centre
NICE	National Institute for Health and Care Excellence
ORPAC	Operating room product approval committee
PARTNER	Placement of AoRTic TraNscathetER Valves (trial)
PVR	Paravalvular regurgitation
RCT	Randomized controlled trial
RPV	Régurgitation paravalvulaire
RVAC	Remplacement valvulaire aortique chirurgical
SAVR	Surgical aortic valve replacement
STS	Society of Thoracic Surgery
SuAVR	Sutureless surgical aortic valve replacement
TAU	MUHC Technology Assessment Unit
TAVI	Transcatheter aortic valve implantation
USI	L'unité de soins intensifs

EXECUTIVE SUMMARY

Background

Surgical implantation of a bioprosthetic valve is the standard treatment for symptomatic severe aortic stenosis. Use of stented bioprostheses, which are designed to remain in position without the need for suturing, can reduce the length and invasiveness of surgery. We were requested by Mr. Gary Stoopler to review the evidence for one such valve, the ATS Enable Sutureless Bioprosthesis Model 6000.

Method

A systematic literature search of PubMed, EMBASE (Ovid), Cochrane, DARE, ISI Web of Sciences with terms specific to the valve and describing the procedure. The search was last updated in April 2013.

Results: Literature review

We found three HTAs and one rapid review of all available valves. There have been no RCTs of sutureless aortic valves versus alternative methods of valve replacement. Nine case series of up to 141 patients have been published, 3 in abstract only. The six fully published articles combined described 348 patients with follow-up generally less than a year.

Thirty-day mortality rate in the 348 patients was 5.2%. Reported adverse events included stroke (2 patients, 0.6%), reoperation for paravalvular regurgitation (PVR) (2%), need for pacemaker (3.7%), and endocarditis during follow-up (1.4%). A separate report described a valve displacement which required surgical repositioning. Valve orifice and gradient were substantially improved.

Two ongoing studies are due to be completed in December 2019 and February 2020, in addition to follow-up on case series already reported.

SuAVR at the MUHC

Nineteen patients have received a sutureless aortic valve (SuAVR) at the MUHC since September 2012, under the Canadian Special Access Program. All were at elevated surgical risk or had anatomic reasons to favour a ministernotomy incision. Implantation required less time than the equivalent procedure for a sutured valve. There have been no deaths or adverse events (stroke or bleeding). One patient had a mild post-operative PVR.

Cost analysis

The SuAVR and AVR devices cost $7,750 and $4,000 respectively. Thus the budget impact of using the former would be $3,750 per case. Possible shorter operating room (OR) time, intensive care unit (ICU) times and hospital stay could result in lower procedure costs to the MUHC. Such savings would not affect the budget impact but would result in increased efficiency.

CONCLUSIONS

- **The evidence for the use of the 3f ATS Enable valve in aortic stenosis is provided by uncontrolled case series involving a relatively small number of published cases (~400 patients), with approximately 1 year follow-up.**
- **MUHC surgeons report that use of SuAVR facilitates partial sternotomy with associated reductions in operation time which may result in improved patient outcomes in selected cases. Optimal patient selection, side effect profile (particularly relative to the more established alternatives), and durability beyond ~1 year remain to be defined.**
- **From the perspective of the MUHC, use of SuAVR via mini-sternotomy instead of SAVR via standard sternotomy will have an increased budget impact of $3,750 per case. Offset savings may result in some increased efficiency.**

RECOMMENDATIONS

- There is insufficient evidence to support the general introduction of the sutureless aortic valve.
- However, there is sufficient evidence of the safety and short term efficacy of the sutureless aortic valve to justify its use for selected patients in a cardiac surgical centre in an academic hospital such as the MUHC. Accordingly, it is recommended that this device receive temporary, conditional approval for use in those patients in whom a conventional surgical procedure is deemed to be high risk but in whom the overall surgical risk is still acceptable.
- Since it is a relatively new procedure a registry including the reasons for case selection, and all pertinent data including operation times and length of hospital stay with follow-up should be maintained, and reviewed in approximately one year.
- Patients should be informed in writing of the lack of information on long-term risks of the sutureless valve.

SOMMAIRE

Contexte

L'implantation chirurgicale d'une bioprothèse valvulaire est le traitement de référence pour une sténose aortique sévère symptomatique. L'utilisation des bioprothèses avec tuteurs, conçues pour rester en position sans avoir recours à des points de suture, peut réduire la durée et le caractère invasif de la chirurgie. L'Unité d'évaluation des technologies du Centre universitaire de santé McGill (CUSM) a été sollicitée par M. Gary Stoopler afin d'examiner les preuves scientifiques liées à l'utilisation de l'une de ces bioprothèses sans suture, l'*ATS Enable Sutureless Bioprosthesis Model 6000*.

Méthodologie

Une recherche systématique de la littérature a été menée dans les bases de données PubMed, Embase (Ovid), Cochrane, DARE et ISI Web of Sciences en utilisant des termes spécifiques reliés à l'utilisation de la valve et la procédure chirurgicale. La dernière mise à jour a été réalisée en avril 2013.

Résultats. Revue de la littérature

La recherche documentaire a permis d'identifier trois rapports d'évaluation des technologies et une revue rapide portant sur tous les types de valves disponibles. Aucun essai clinique randomisé comparant l'utilisation de valves aortiques sans suture à d'autres méthodes de remplacement de valves n'a été identifié. Neuf séries de cas incluant jusqu'à 141 patients ont été publiées dont trois d'entre elles seulement sous forme de résumé. Les six autres séries de cas publiées incluaient 348 patients suivis généralement pendant moins d'un an.

Le taux de mortalité à 30 jours chez ces 348 patients était de 5,2%. Certains événements indésirables ont été rapportés pendant le suivi soit : des accidents vasculaires cérébraux (0,6%), des interventions chirurgicales pour traiter des régurgitations paravalvulaires (RPV) (2%), des besoins pour un stimulateur cardiaque (3,7%) et la survenue d'endocardites (1,4%). Un déplacement de la valve ayant nécessité un repositionnement chirurgical a également été décrit dans un rapport distinct. Des améliorations substantielles au niveau de la surface de la valve et du gradient de pression ont été rapportées.

En ajout du suivi des séries de cas déjà rapportées, deux études en cours sont prévues être complétées en décembre 2019 et février 2020.

Remplacement valvulaire aortique chirurgical sans suture au CUSM

Dix-neuf patients ont subi un remplacement valvulaire aortique chirurgical (RVAC) sans suture au CUSM depuis septembre 2012, grâce au Programme d'accès spécial de Santé Canada. Tous les patients étaient à risque chirurgical élevé ou

présentaient des caractéristiques anatomiques qui orientaient la décision de pratiquer une sternotomie partielle (mini-sternotomie). L'implantation de la bioprothèse sans suture a pris moins de temps que la procédure équivalente avec une valve suturée. Aucun décès ou événement indésirable (accident vasculaire cérébral ou hémorragie) n'a été rapporté. Un patient a présenté une légère RPV postopératoire.

Analyse des coûts

Les bioprothèses valvulaires utilisées pour un RVAC avec ou sans sutures coûtent 4000 $ et 7750 $, respectivement. Ainsi, l'impact budgétaire de l'utilisation d'une bioprothèse sans suture serait de 3750 $ par patient. Une éventuelle diminution du temps requis en salle d'opération (OR) et à l'unité de soins intensifs (USI), et de la durée d'hospitalisation pourrait entraîner une baisse des coûts de la procédure pour le CUSM. Ces économies n'auraient pas d'impact budgétaire mais pourraient se traduire par une efficacité accrue.

CONCLUSIONS

- **Les preuves scientifiques liées à l'utilisation de la *3f ATS Enable valve* dans le traitement de la sténose aortique sont basées sur des séries de cas non contrôlées impliquant un nombre relativement faible de patients (environ 400 patients) suivis approximativement pendant 1 an.**
- **Les chirurgiens du CUSM ont mentionné que l'utilisation des bioprothèses sans suture facilite la sternotomie partielle résultant en des réductions de la durée opératoire qui peuvent améliorer les résultats chez certains patients. La sélection optimale des patients, le profil d'effets secondaires (en particulier comparativement aux procédures alternatives déjà établies) et la durabilité au-delà d'environ un an restent à définir.**
- **Pour le CUSM, la pratique du RVAC sans suture par mini-sternotomie comparativement au RVAC avec suture par sternotomie augmenterait les coûts de 3,750 $ par patient. Les coûts d'opportunités pourraient entraîner une augmentation de l'efficience.**

RECOMMANDATIONS

- **Les preuves sont insuffisantes pour recommander l'introduction générale de la valve aortique sans suture.**
- **Cependant, il y a suffisamment de preuves sur l'innocuité et l'efficacité à court terme de la valve aortique sans suture pour justifier son utilisation pour des patients sélectionnés dans un centre de chirurgie cardiaque d'un hôpital universitaire comme le CUSM. En conséquence, il est recommandé que ce type de valve reçoive une approbation conditionnelle temporaire pour une utilisation chez les patients pour lesquels une intervention chirurgicale conventionnelle est jugée à risque élevé, mais pour qui le risque chirurgical global demeure acceptable.**

- **Comme il s'agit d'une procédure relativement nouvelle, la tenue d'un registre comprenant les raisons expliquant la sélection des cas et toutes les données pertinentes, incluant les durées opératoires et de séjour à l'hôpital et le suivi, doit être maintenue et révisée approximativement dans un an.**
- **Les patients doivent être informés par écrit de l'absence d'information sur les risques à long terme liés à l'utilisation de la valve sans suture.**

Surgical aortic valve replacement with the ATS Enable® sutureless aortic valve for aortic stenosis

1. BACKGROUND

Aortic valve replacement (AVR) is the standard of care for patients with severe and/or symptomatic aortic stenosis, but patients who are elderly or who have multiple comorbidities may be at unacceptably high risk of death or disability from surgery. Surgical sutureless fixation of replacement valves has been a subject of research interest since the 1960s[1,2]. The sutureless valve can when necessary be implanted via a partial sternotomy, thus reducing the risk of sternal dehiscence and infection. It is also reported to reduce cross-clamping time and time on cardiopulmonary bypass, which would favour improved clinical outcomes[3].

The ATS Enable Sutureless Bioprosthesis Model 6000 (ATS Enable) was developed from the ATS 3f Aortic Bioprosthesis Model 1000 (ATS 3f)[4]. Both valves are constructed from a tube of treated equine pericardium, which is fixed at three equidistant points around its circumference. During diastole, the free flaps collapse inwards, appose, and seal. The Model 1000, the valve currently inserted using open heart surgery, is stentless and must be sutured in place. The Model 6000 was created by adding a stent made of nitolol, an alloy which becomes malleable when chilled.

The TAU received a request to review the ATS Enable Sutureless Bioprosthesis Model 6000 from Mr. Gary Stoopler, Administrative Director, Surgical Division, MUHC, following a request to the Operating Room Product Approval Committee (ORPAC) by Dr. de Varennes, Head of Cardiovascular Surgery.

2. OBJECTIVE(S)

- To assess the efficacy and safety of aortic valve replacement with a sutureless aortic valve (SuAVR) in patients with aortic valve stenosis, and estimate the costs of this procedure to the MUHC.
- To review the use and outcomes of SuAVR at the MUHC.

3. METHODS

3.1. Literature search

One author (AS) carried out a systematic literature search in the Cochrane Collaboration database, the Database of Abstracts of Reviews of Effects (DARE), PubMed, EMBASE (Ovid), ISI Web of Science (for abstracts). Search terms were used for the specific bioprosthesis, “ATS Enable” with “6000”, “bioprosthesis” and “sutureless”, and for the procedure “sutureless” and “aortic valve replacement” or “aortic valve implantation”. The latter two were mapped to indexed terms, as available. The search was limited to articles on human subjects, in English and French, published since 2005. The search was last updated on April 24, 2013.

We also searched clinical trials registries ClinicalTrials.gov (www.ClinicalTrials.gov) and Current Controlled Trials (www.controlled-trials.com) for ongoing or upcoming studies, and scanned the bibliographies of all retrieved publications.

3.2. Cost analysis

We compared the procedure costs of SuAVR versus conventional surgical AVR (SAVR). We estimated costs from the perspective of the MUHC. This estimate included the costs of purchasing types of valves, operating room (OR), nurse, anaesthesia technician, intensive care unit (ICU) stay, coronary care unit (CCU)stay, and hospitalization. We also performed a univariate sensitivity analysis and probabilistic sensitivity analysis by running 10,000 iterations. 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 1 for details.

4. RESULTS

4.1. Efficacy and safety

The search retrieved one rapid review[5] of sutureless valves, and health technology assessments from Australia[6] and New Zealand[7]. The National Institute for Health and Care Excellence (NICE) has published an overview[8], and released a draft consultation document (due July 2013) for public comment[9]. A total of 9 reports of case series were retrieved, either as full papers[10-15] or in abstract[16-19]. Only the latest update of a series was included, with the exception of one abstract[19] which updated an earlier paper[15]. One report[13] featured a non-randomized comparison of 27 of patients undergoing surgical aortic valve replacement with ATS Enable with 29 patients undergoing implantation of an Edwards SAPIEN valve via the transapical route (TAVI) at the same institution.

4.1.1. Case series

The nine reports retrieved are summarized in Table 2 and Table 3, and include procedures in up to 410 patients. There is possibly some overlap between two studies[7,10] (We did not receive an answer to our enquiry from the authors). Follow-up is generally a year or less and safety outcomes are incompletely reported. Nevertheless, some tentative conclusions can be drawn:

1). First, the procedure appears to be relatively safe in this high risk group of patients. Of the 348 patients reported in full articles, there were 18 deaths (5.2%) in the first 30 days, and a total of 37 deaths in all followed-up cases (10.6%). For comparison, 30-day mortality following the TAVI procedure in clinically comparable cases in the PARTNER A and B reports was 3.5%[20] and 5.0%[21], respectively.

2). Second, the complication rate was not excessive. Of the 348 patients, seven patients developed sufficiently severe paravalvular regurgitation (PVR) to require surgery (2%), and two patients had a stroke (0.6%). Five patients (1.4%) developed endocarditis during follow-up, with three requiring surgical explantation, and 13 received a pacemaker (3.7%). However, it cannot be assumed that all reports included all complications.

In addition to the adverse events described in the case series (Table 3), a recent case report[22] described a 78-year-old woman who developed haemolysis and congestive heart failure three months after receiving an ATS Enable valve. The valve had displaced upward into the outflow tract with the development of severe PVR. At the original surgery, the annulus was extensively decalcified, which may have contributed to a misplacement of the valve. Upon reoperation, the same valve was repositioned and secured with sutures, and the patient recovered

3). Third, the time taken for this procedure appears not to differ greatly from SAVR, and in some aspects may be reduced. In the reports of SuAVR summarised in Table 2, aortic cross clamp (ACC) time ranges from 37-67 minutes. By comparison, recent retrospective analyses of patients undergoing SAVR reported average cross clamp times of 53±17 minutes[3], 68±26 minutes[23], and 55±14 minutes[24]. Dr. de Varennes, who is experienced in both techniques, finds that aortic cross-clamp time and time for deployment of prosthesis are markedly less than those required for SAVR (personal communication).

4). Finally, as might be expected, it is clear from these reports that the procedure effectively relieves stenosis and causes significant functional improvement.

Comment. The length of follow-up was less than one year for all the reported studies except that of Wendt et al, 2009[19], who described (in abstract), a 3-year follow-up for 4 patients who received the first generation bioprosthesis. All were still alive, in NYHA Class I. One had a stable PVR. Sadowski et al, 2009[12] described 27 patients aged 60 to 78 years who received valves between 2005 and 2009, with follow-up of 3 months to 4.5 years. One patient required re-operation on post-

operative day 4 for a PVR. The authors and institution also participated in the Martens study[10], so it is possible there is overlap of later patients.

In the non-randomized comparison reported by Doss et al, 2012[13], the patients undergoing SuAVR (n=27) were younger by nearly seven years than those undergoing transapical TAVI (n=29), 78 versus 84.7 years. They also had a markedly lower mean logistic EuroSCORE (13.7% versus 35.3%), reflecting significantly less respiratory, cardiovascular, and renal disease. Unadjusted in-hospital mortality was lower in those with SuAVR (11% versus 17%). No patients in either group experienced a stroke. Longer-term outcomes were not compared.

4.1.2. Systematic reviews and health technology assessments

The rapid review by Sepehripour et al[5] identified six uncontrolled case series, three of which used the ATS Enable valve. Two of the three are included in Table 1. There was patient overlap between Martens et al, 2011[10] and Martens et al, 2009[25], with the latter reporting on single centre experience within the multicentre study[11]. When the pooled outcomes for all valves were compared with results of conventional surgical aortic valve replacement as reported in the PARTNER trial[20] the outcomes of sutureless aortic valves were found to "compare favourably with conventional valves in terms of mortality, neurological deficit, renal failure and post operative bleeding", while there was an "increased incidence of endocarditis and paravalvular leak (PVR), together with raised mean valve gradients."

The overview prepared for NICE[8] included the studies by Martens et al, 2011[10], and Sadowski et al, 2009[12], in their primary analysis (which covered all available valves). Their interventional procedure guidance document[9], which includes recommendations, has undergone public consultation and is due to be released in July 2013.

The Australian reviewers (ASERNIP/S)[6] concluded that "the sutureless AVR devices appear to be safe, with a small proportion of patients experiencing paravalvular leaks and thromboembolic events" but noted the lack of comparative data and planned studies comparing SuAVR and SAVR. In the opinion of the reviewers from the New Zealand National Health Committee[7], "there is insufficient evidence available at this time ... to assess sutureless AVR," and it should be used only be under trial conditions.

4.2. Upcoming studies

The case series described by Martens et al, 2011[10], is ongoing but not recruiting (ClinicalTrials.gov NCT01116024)[26], with an estimated completion date of August 2014. An extension study of 100 patients with planned follow-up of out to ten years is currently recruiting (NCT01636648)[27], with a projected study completion date of December 2019. A large (800 patients) post-marketing study of outcomes out to 5

years (NCT01720342)[28] started recruiting February 2013, with projected completion date for primary data collection February 2020.

4.3. Economic evaluations

We did not retrieve any published economic analyses.

5. SUTURELESS AVR AT THE MUHC

5.1. MUHC SuAVR experience to date

Between September 2012 and April 2013, 19 patients have undergone surgical aortic valve replacement with an ATS Enable valve under the Health Canada Special Access Program for Medical Devices[29]. All patients had high (Society for Thoracic Surgery (STS) score ≥10%) or intermediate surgical risk (STS 4-10%) for surgical aortic valve replacement, or had anatomic reasons to favour a ministernotomy (moderate/severe truncal obesity, severe COPD, recent chest wall trauma). Additional indications were prior implantation of a mitral valve prosthesis, which is a contraindication for TAVI, and avoiding an aortic root enlargement procedure (with prolongation of the operation and potential for complications) in patients with a small aortic annulus. Patients with more than 5 years life expectancy were also eligible.

Procedural success was 100%, with no deaths to date in follow-up. Eleven patients (57.9%) underwent ministernotomy, and 4 underwent concomitant coronary artery bypass grafting. Nine to 18 minutes were required for aortotomy, debridement of the calcified valve, and deployment of the prosthesis, a reduction of 50-75% (B.de Varennes, personal communication) of the corresponding time for the implantation of a sutured valve. Patients spent a median 1 day (mean 1.2 days) in ICU. There were no adverse events of stroke or bleeding. One patient had a mild PVR.

5.2. Cost analysis

The SuAVR and AVR devices cost $7,750 and $4,000 respectively. Thus the budget impact of replacing AVR by SuAVR would be $3,750 per case.

Possible shorter OR time, ICU times and shorter hospital stay could result in reduced procedure costs to the MUHC. Although direct comparisons of these times are not available, a meta analysis of four RCTs comparing mini-sternotomy with full sternotomy for aortic valve surgery found that mini-sternotomy was associated with shorter ICU time (-0.57 days. P=0.003)[30]. Hospital stay was also shorter, but the difference is not significant (-2.03 days. P=0.06). Dr deVarennes has estimated that use of SuAVR shortens OR time by 2 hours. Assuming hospital stay following SuAVR via mini-sternotomy to be 1.5 days less than SAVR via full sternotomy and a reduction of 2 hours of OR time, the procedure costs (excluding drugs, tests, and

physicians costs) to the MUHC would be $18,796, and $17,395 for SuAVR and SAVR, respectively .

The average ICU time for the first 19 MUHC SuAVR patients was 1.2 days compared to a mean±standard deviation of 3.6±8.1 days for 853 patients undergoing AVR via standard sternotomy. Using this difference the procedure cost for SuAVR would be $15,666 compared to $17,395 for SAVR. Note that any such savings would not affect the budget impact but would result in increased efficiency.

Univariate sensitivity analyses for the original analysis that varied the inputs by 25% produced incremental costs of -$537 to $3,338 for SuAVR versus SAVR, with the widest range produced by variation in the costs of the sutureless valve. Probabilistic sensitivity analyses produced incremental costs of $1,397±$605 (mean±standard deviation) for SuAVR versus SAVR.

For further details see Appendix 1.

Table 1 Cost analysis of SuAVR versus SAVR (per patient)

	SuAVR	SAVR	Incremental cost (SuAVR vs. SAVR)
Cost of procedure and hospitalization	11,046	13,395	--
Cost of valve, catheter, etc.	7,750	4,000	--
Sum	18,796	17,395	1,401

All costs were expressed in $CAD 2013.

6. CONCLUSIONS

- **The evidence for the use of the 3f ATS Enable valve in aortic stenosis is provided by uncontrolled case series involving a relatively small number of cases (~400 patients), with approximately 1 year follow-up.**
- **MUHC surgeons report that use of SuAVR facilitates partial sternotomy with associated reductions in operation time which may result in improved patient outcomes in selected cases. Optimal patient selection, side effect profile (particularly relative to the more established alternatives), and durability beyond ~1 year remain to be defined.**
- **From the perspective of the MUHC, use of SuAVR via mini-sternotomy instead of SAVR via standard sternotomy will have a budget impact of $3,750 per case. Offset savings may result in some increased efficiency.**

7. RECOMMENDATIONS

- There is insufficient evidence to support the general introduction of the sutureless aortic valve.
- However, there is sufficient evidence of the safety and short term efficacy of the sutureless aortic valve to justify its use for selected patients in a cardiac surgical centre in an academic hospital such as the MUHC. Accordingly, it is recommended that this device receive temporary, conditional approval for use in those patients expected to most benefit.
- Since it is a relatively new procedure a registry including the reasons for case selection, and all pertinent data including operation times and length of hospital stay with follow-up should be maintained, and reviewed in approximately one year.
- Patients should be informed of the lack of information on long-term risks.

TABLES

Table 2 Case series using ATS Enable in surgical valve replacement for aortic stenosis: patients and operative detail

Reference Study location	N	Age Years, mean±SD	Male n (%)	EuroSCORE %	Surgical Approach	ACC Minutes, mean±SD	CPB Minutes, mean±SD
Full text							
Eichstaedt 2013[14] Oldenberg, Germany	120	76.7±5.9	81 (68%)	20.1±19% (range 2-90%)	Ministernotomy/minithoracotamy 24 (59%); others not stated. Isolated AVR 71 (59%). Other procedures 49 (41%)	Isolated AVR 37±18; other 47±19	Isolated AVR 62±18; other 80±39.
Doss 2012[13]	27	78±4	11 (41%)	13.7±6.3	Ministernotomy (isolated AVR) or median sternotomy	66±23	100±32
Martens 2011[10] Europe (10 centres)	140	76.1±5.7	53 (38%)		Sternotomy 112 (80%) Ministernotomy 80 (20%)	58.1±21.5	84.9±32.4
Aymard 2010[11] Switzerland.	28	75.7±6.6 (range 72-89)	10 (36%)	7.1±1.8	Sternotomy 22 (79%) Ministernotomy 6 (21%)	39±15	58±20
Sadowski 2009[12] Poland	27	69.5 (range 60-78)	16 (59%)		Sternotomy 27 (100%)	About 30	
Wendt 2008[15], updated in abstract 2009[19] Germany	6	74±1.8	3 (50%)		Sternotomy 6 (100%)	56±24	87±32
Abstracts							
Concistre, 2012[16] Germany/Italy	32 Enable (of 126)			11.2±8.5	Minithoracotomy 78 (62%), Sternotomy 48 (38%).	76.4±16.7	

Reference Study location	N	Age Years, mean±SD	Male n (%)	EuroSCORE %	Surgical Approach	ACC Minutes, mean±SD	CPB Minutes, mean±SD
Concistre, 2012[17] Italy	18	77.6 (range 71-86).	4 (22%)	13.6±11.9	Ministernotomy 13 (72%), Minithoractomy 5 (28%)	67.4±18.1	100.6±23.1
Lall, 2011[18] UK	12	75	6 (50%)	14±3.4	Ministernotomy	45±5	66±11

NYHA, New York Heart Association. PVG, perivalvular leak. TVG, transvalvular gradient.

Table 3 Case series using ATS Enable in surgical valve replacement for aortic stenosis: outcomes

Reference Study location	N	Follow-up	Mortality n (%)	Complications n (%)	Valve measurements mean±SD
Full text					
Eichstaedt 2013[14] Oldenburg, Germany	120	93.5 patient-years; mean 313 days	30-day: 8 (6.7%). Late: 3 (2.5%) Total: 11 (9.2%)	Reintervention required: 30-day 2 (1.7%; Iatrogenic dislocation of valve 1. PVR 1). Late 3 (2.5%; Endocarditis 1, PVR 1). PVR 6 (5%; Including 2 above). Stroke 1 (0.8%). Thromboembolism due to HIT 1 (0.8%). Renal failure 2 (1.7%). Endocarditis 2 (1.7%, including above). Pacemaker 8 (6.7%).	12-months: AVA 2.2±0.8 cm^2. AVG 9.5±3.8 mmHg
Doss 2012[13]	27		In hospital: 3 (11%)	Conversion to sutured valve, 2 (7.4%). Stroke, 0. Heart-block 0.	
Martens 2011[10] Germany, Poland, Switzerland	140	121 patient-years.	30-day: 5 (3.6%) Late: 13 (9.3%; valve-related 2) Total: 18 (12.8%)	Early: Reintervention for PVR 3 (2.1%). Stroke 1 (0.7%). Minor PVR 3 (2.1%). Late: Endocarditis 3 (2.1%; valve surgically removed in 2).	11-14 months: Effective orifice area 1.67±0.44 cm^2. AVG 8.62±3.16 mmHg
Aymard 2010[11] Switzerland.	28	18 months.	30-day: 2 (7%). Late: 2 (7%). Total: 4 (14%)	PVR 3 (11%; valve removed 1). Pacemaker 5 (18%).	12 months: AVA 2.1±0.4 cm^2. AVG 11±2 mmHg.
Sadowski 2009[12] Poland	27		0	Conversion to sutured valve 3 (11%). PVR 2 (7%; requiring surgery 1). Endocarditis 0.	12 months: AVG 6.0 mmHg.

Reference Study location	N	Follow-up	Mortality n (%)	Complications n (%)	Valve measurements mean±SD
Wendt 2008[15], updated in abstract 2009[19] Germany	6	Up to 3 years (n=4)	In-hospital: 0. Late: 1 (17%) Total: 1 (17%)	PVR 2 (33%; reoperation required 1). Transient renal failure 1 (17%).	12-months: AVG 6.8±3.5 mmHg. AVA 2.2±0.5 cm^2.
Abstracts					
Concistre 2012[16] Germany/Italy	32 Enable (of 126)	8.3	In-hospital Enable: 1 (3.1%)	Repeat surgery Enable 1 (3%).	AVG 11.2±5.2 mmHg
Concistre 2012[17] Italy	18	4 months	0	PVR 3 (17%).	End follow-up: AVG 10.8 mmHg
Lall 2011[18] UK	12		0	No major morbidities.	End follow-up: AVG 11.1±2.6 mmHg

AVA, aortic valve area; AVG, aortic valve gradient; HIT, heparin-induced thrombocytopenia; PVR, paravalvular regurgitation.

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APPENDICES

Appendix 1 Cost analysis

We estimated from the perspective of the MUHC the following costs for SuAVR and SAVR: valves, operating room (OR), nursing, anaesthesia technician, ICU stay, CCU stay, and hospitalization. We excluded the costs for medications, tests which we assumed to be comparable, and physician fees which are not a cost to the hospital in Quebec. The estimates of the average healthcare resource uses (OR time, ICU stay, CCU stay etc.) were derived from analyses of 853 surgical valve procedures conducted between 2008 and 2012 at MUHC (see Table 4). Due to lack of resource use data for SuAVR, we assumed that besides a reduction of 2 hours of OR time, and 1.5 days of post-operative hospital stay associated with SuAVR, the resource uses by SuAVR are same as these for SAVR. The reductions of OR time and hospitalization were estimates of Dr. de Varennes.

In addition to estimating the incremental costs of SuAVR versus SAVR, we performed a univariate sensitivity analysis by changing by ±25% the mean key parameters impacting the incremental cost. We also performed probabilistic sensitivity analysis by running 10,000 iterations. 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 SuAVR and SAVR

	Mean	Distribution*	Reference†
Resource use for sutureless valve replacement*			
Anesthesia technician (hours)	2.62	Normal (2.62, 0.08)	Estimate
Operating room (hours)	2.68	Normal (2.68, 0.08)	Estimate
Cardiology unit, including CCU stay (days)	0.76	Gamma (36, 0.02)	MUHC
ICU stay (days)	3.63	Gamma (169, 0.02)	MUHC
Post-operative hospital stay (days)	10.22	Normal (10.22, 0.59)	Estimate
Resource use for surgical valve replacement*			
Anesthesia technician (hours)	4.62	Normal (4.62, 0.08)	MUHC
Operating room (hours)	4.68	Normal (4.68, 0.08)	MUHC
Cardiology unit, including CCU stay (days)	0.76	Gamma (36, 0.02)	MUHC
ICU stay (days)	3.63	Gamma (169, 0.02)	MUHC
Post-operative hospital stay (days)	11.72	Normal (11.72, 0.59)	MUHC
Price of valve, catheter, cannula and other disposable ($ CAD 2013)*			
The devices for sutureless valve therapy in total	7,750	Fixed	MUHC
The devices for surgical valve therapy in total	4,000	Fixed	MUHC
Unit price of healthcare resource ($ CAD 2013)			
Operating room per hour	884	Fixed	MUHC
ICU stay per day	1,288	Fixed	MUHC
Hospitalization (Surgical Nursing) per day	338	Fixed	MUHC
Cardiology unit, including CCU per day	593	Fixed	MUHC
Technician fees of anesthesia per hours	37	Fixed	MUHC
Nurse per hour	33	Fixed	MUHC

† Length of stay for SAVR was supplied by D. Dubé. Operating room time for SAVR was supplied by E. Balok. Unit costs were supplied by N. Robert. Estimates of SuAVR procedure time were supplied by B. de Varennes.

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