TITLE: Percutaneous Heart Valves for Valvular Heart Disease: An Updated Review of the Clinical and Cost-Effectiveness and Guidelines

DATE: 30 April 2010

CONTEXT AND POLICY ISSUES:

An estimated 30% of heart surgeries are attributable to valvular heart disease, a common cause of cardiovascular morbidity and mortality. Increasingly, patients who require heart valve replacement are of advanced age and have comorbidities and poor health. Because of this, many are not candidates for conventional surgery for heart valve replacement, which involves extracorporeal circulation and partial or complete opening of the chest.

In recent years, there have been a number of surgical techniques developed to reduce surgical trauma associated with valve replacement, one being the use of the percutaneous route for heart valve repair and replacement. Percutaneous heart valve replacement involves delivering a biological or synthetic replacement valve through the vasculature into position in the heart using a catheter, guidewire, and visual guidance. For aortic valve replacement, the valve can be inserted via retrograde catheterization of the femoral artery or directly into the left ventricle through a chest wall incision (trans-apical approach). This procedure is referred to as TAVI (transcatheter aortic valve implantation).

Two percutaneous aortic valves are used clinically, Edwards-Sapien (Lifesciences, Irvine CA, USA) and CoreValve (Medtronic, Minneapolis, MN, USA), neither of which are licensed for use in Canada. Both can be used under special access regulations in Canada. The replacement valves are comprised of collapsible stent frames with animal pericardial valve leaflets.

The pulmonary valve can also be replaced percutaneously in patients with congenital right ventricular outflow tract disorders. Children with these disorders often require surgical repair early in life and repeat surgeries throughout their lifetimes. Percutaneous pulmonary valve replacement is a technique that can postpone repeat surgery or decrease the number of surgical “redos” required in the patient’s lifetime. The Melody (Medtronic, Minneapolis, MN, USA) peripheral pulmonary valve is the most commonly used in clinical practice and has been...
licensed in Canada since December of 2006.\textsuperscript{4} It is inserted via the femoral vein using standard right heart catheterization techniques.\textsuperscript{3}

Information on the potential benefit and harms associated with percutaneous heart valves may help to better understand the place of this technology in the management of valvular heart disease. This report is an update to a previous rapid response\textsuperscript{5} on the clinical and cost-effectiveness of percutaneous heart valve replacement that was completed in January of 2010.

**RESEARCH QUESTIONS:**

1. What is the clinical effectiveness of percutaneous heart valves for the treatment of patients with valvular heart disease?

2. What is the cost-effectiveness of percutaneous heart valves for the treatment of patients with valvular heart disease?

3. What are the guidelines for the use of percutaneous heart valves for patients with valvular heart disease?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including Medline, The Cochrane Library (Issue 4, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between December 1, 2009 and April 12, 2010, as this was an update to a previous rapid review of the literature based on a search from 2004 to December 2009.\textsuperscript{5} Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, economic studies and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports are presented first. These are followed observational studies. Observational studies without comparison groups were excluded from this report since studies of higher levels of evidence were available. This same selection criteria was applied in the previous rapid response review on percutaneous heart valves.\textsuperscript{5}

**SUMMARY OF FINDINGS:**

One health technology assessment report\textsuperscript{2} and three observational studies\textsuperscript{6-8} were identified in this update. Results of one registry study\textsuperscript{9} that included data from six Canadian centres is included in the Appendix.

**Health technology assessments**

In 2009, the Technology Assessment Unit of the McGill University Health Centre (MUHC) assessed the clinical benefit and potential harm associated with TAVI through a systematic literature review and assessment of clinical data from the first 12 patients who underwent the
procedure at their centre. Individual studies were identified through searches of MEDLINE and EMBASE online databases. The database searches were limited to English and French publications from 2002 onward. There was no restriction on study design, but studies had to be published in peer-reviewed journals and case series reports had to include 10 or more cases in order to be included. Further, in order to be included, the surgical insertion of the valve had to involve trans-femoral or trans-apical routes. Studies which used a trans-septal approach to valve insertion were excluded as this approach is no longer used in practice. Online databases of HTA reports were also searched to identify any existing reports.

The search identified three systematic reviews, one guidance document from the National Institute for Clinical Excellence, and 17 research publications, 16 of which were described as case series reports (n=616) and one of which was described as a report from a multicentre registry (n=646). Across the 17 publications, data from 1262 patients were available. Data from the 16 case series were pooled to determine the mortality rate at 30 days, the late mortality rate, functional improvement, and complication rate. In addition to the published data, unpublished data were also obtained from the SOURCE Registry, which includes 30 day follow-up data on 1380 TAVI’s performed at 32 centres in Europe, and from the Canadian Transcatheter Aortic Valve Implantation Program (CTAVIP), which included 339 TAVI’s performed in six hospitals in Canada. Outcomes of the 12 cases undergoing TAVI at MUHC were also reported. The outcome data from the various data sources are listed in the Table 1.

Table 1: Outcomes from the Data Sources Included in the MUHC TAVI Report

<table>
<thead>
<tr>
<th>Case Reports (16 studies of 616 patients)</th>
<th>Registry Report (1 study of 646 patients)</th>
<th>SOURCE Registry (1380 patients)</th>
<th>CTAVIP (339 patients)</th>
<th>MUHC Cases (12 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success Rate*</td>
<td>93%</td>
<td>97%</td>
<td>94%</td>
<td>Not reported</td>
</tr>
<tr>
<td>30-day Mortality</td>
<td>10%</td>
<td>8%</td>
<td>8.5%</td>
<td>10.4%</td>
</tr>
<tr>
<td>Late Mortality</td>
<td>Six Months (assessed in 6 studies): Range: 3% to 26% - data not pooled</td>
<td>Not reported</td>
<td>Not reported</td>
<td>One Year: 24% Two year: 35%</td>
</tr>
<tr>
<td>Functional Improvement</td>
<td>80% to 100% in those cases that reported this outcome - data not pooled</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Complications</td>
<td>Described as variable and expected in 25% to 30% of procedures</td>
<td>Not reported</td>
<td>Major access site complication: 7% Valve migration, malposition, embolisation: 1.8%</td>
<td>Major access site complication: 13% Valve migration, malposition, embolisation: 7%</td>
</tr>
</tbody>
</table>
The authors of the MUHC TAVI report stated that the systematic reviews that they included in their report differed in their conclusions, with one report stating that TAVI should receive provisional recognition for insurance and another stating that because of safety concerns and a lack of a well defined target population, reimbursement of TAVI could not be defended.

Based on the included cases series and registry data, the authors of the report summarized that TAVI could be carried out with an expected mortality rate of 8% to 10% at 30 days, but that the mortality rate at one to two years was much less certain. They further stated that serious, but manageable complications could be expected in 25% to 30% of cases. They went on to conclude that TAVI is a feasible procedure that can provide relief of symptoms in those that survive, but did note that the mortality risk was high and the long-term prognosis was uncertain. The mortality rate in the absence of TAVI was described as unknown due to the lack of data from randomized controlled studies.

The main limitations of this report were its lack of detail in reporting methods used to select studies for inclusion, assess quality of the included studies, and pool data for the analysis. Further, the quality of the included studies was low (case series), which could compromise the validity of the report’s findings.

### Observational studies

In 2010, Bagur et al.\(^6\) published a study of the incidence and prognostic value of acute kidney injury in patients undergoing TAVI (n=213). The study population included patients with symptomatic severe aortic stenosis who had TAVI performed at St. Paul’s Hospital in Vancouver or at the Quebec Heart and Lung Institute in Quebec City from January 2005 and February 2009. Patients who required chronic hemodialysis were excluded from the study, as were those participating in another ongoing TAVI trial and those who died within 24 hours following TAVI. There was no comparison group included for this analysis, so the findings are

<table>
<thead>
<tr>
<th></th>
<th>Case Reports (16 studies of 616 patients)</th>
<th>Registry Report (1 study of 646 patients)</th>
<th>SOURCE Registry (1380 patients)</th>
<th>CTAVIP (339 patients)</th>
<th>MUHC Cases (12 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Average Net Cost per Patient: $24,024</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Budget Impact: $720,719 annually</td>
</tr>
</tbody>
</table>

NYHA: New York Heart Association Class

* Success Rate refers to whether the valve was inserted successfully

---

Percutaneous Heart Valves for Valvular Heart Disease
not summarized in this HTIS report. As a part of this study, however, the incidence of acute kidney injury in a subgroup of patients with pre-existing chronic kidney disease undergoing TAVI (n=119) was compared to those undergoing surgical aortic valve replacements (SAVR) (n=104).

For the comparison to SAVR, the TAVI group consisted of a subgroup (i.e., those with pre-existing kidney disease; n=119) of the 213 patients. Pre-existing kidney disease was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m². The comparison group consisted of 104 consecutive patients with severe aortic stenosis and pre-existing kidney disease who had SAVR at the Quebec Heart and Lung Institute during the same time frame. The Edwards-Sapien or Cribier–Edwards valves were used in the TAVI group and were inserted via the transfemoral (52%) and transapical approaches (48%). SAVR procedures were performed by accessing the heart via a mid-sternotomy and standard surgical techniques while using extracorporeal circulation. Patients were classified as having acute kidney injury if their eGFR decreased by 25% or more in the first 48 hours following the surgery or if hemodialysis was needed during hospitalization.

The average age of the TAVI group was 83 ± 7 years compared to 74± 8 years in the SAVR group (p<0.0001). In both groups, the majority of patients were female (59% of the TAVI group and 52% of the SAVR group). The baseline Logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation - a measure of percent predicted operative mortality in cardiac surgery)¹⁰ in the TAVI group was 31.2± 18.1 compared to 21.8± 14.6 in the SAVR group (p<0.0001). Approximately 9.2% of the TAVI group had acute kidney injury following surgery compared to 25.9% of the SAVR group (OR: 0.29, 95% CI: 0.14 to 0.62, p <0.001). In a propensity score adjusted analysis the odds ratio was 0.33 (95% CI: 0.13 to 0.79, p< 0.014). The propensity score made an adjustment for the following variables: age, logistic EuroSCORE, congestive heart failure, coronary artery disease, peripheral vascular disease, and baseline eGFR.

Approximately 2.5% of the TAVI group required dialysis during hospitalization compared to 8.7% of the SAVR group (p=0.07). After matching on baseline eGFR, the difference became statistically significant, although only 64 patients in each group were matched for this analysis. The authors concluded that the incidence of acute kidney injury in patients with pre-existing kidney disease was lower following TAVI than SAVR.

The authors of this study identified a number of limitations. One limitation was that, while the data were collected prospectively in a database, this study was a post-hoc analysis of those data that had not been pre-specified. They acknowledged the possibility that confounding variables may not have been included in the analysis and that this may have affected their results. Categorization as having acute kidney injury was based on a single measurement 48 hours after surgery. The authors felt that additional cases of acute kidney injury could have been identified if this was assessed again during the hospitalization. The authors indicated that these results needed to be confirmed with a randomized design. Additionally, there were baseline differences between groups, but they did try to adjust for these statistically.

While the study sites were Canadian, the authors stated that similar results might not be expected in low volume centres or to surgeons with less experience. As well, the study excluded patients who were already enrolled in a different TAVI study, so it is not clear if the population would be considered representative of the broader population with severe aortic stenosis.
Kahlert et al., 2010\textsuperscript{7} compared the incidence of cerebral ischemia in patients undergoing TAVI (n=32) to a historical control group of patients who underwent SAVR (n=21). The TAVI group consisted of patients who underwent surgery between September 2007 and March 2009 at a single centre. Both the Edwards Sapien valves (n=22) and CoreValves were used (n=10) in the procedures. It was not clear whether the transapical or transfemoral approach was used. The patients in the SAVR group were retrospectively identified from a previous study. It was not clear if this study took place at the same centre. At the study centre, patients with severe aortic valve stenosis and logistic EuroSCORE of 20 or higher or were deemed to be too high risk for SAVR due to comorbidities and other risk factors not included in the EuroSCORE were considered for TAVI. Patients underwent a neurological exam before the procedure, after the procedure once anesthesia was completely reversed, and three months after the procedure. Cerebral diffusion weight magnetic resonance imaging was performed at baseline, post-procedure, and after three months to identify cerebral ischemia.

The average age of the Edwards Sapien and CoreValve groups were 78.3 (76.4–80.2) years and 83.8 (79.2– 88.4) years, respectively, compared to 67.4 (63.9 –70.8) years in the SAVR group (p<0.001). The logistic EuroSCOREs were as follows: Edwards Sapien: 22.8 (16.5–29.2); CoreValve: 17.9 (12.0–23.7) and SAVR: 2.5 (1.8–3.2); p<0.001, indicating the predicted percent perioperative mortality was significantly higher in the patients undergoing TAVI. The post-procedural neurological examination was performed an average of 3.4 days following surgery and revealed no changes from baseline. Post-procedural MRI revealed new foci of restricted diffusion more frequently in both of the TAVI groups compared to the SAVR group. On the three month follow-up MRI there were no new foci of restricted diffusion in any patients and there were no changes to the clinical neurological exam. The authors concluded that TAVI is associated with a high incidence of foci of restricted diffusion on MRI, but that these foci were not associated with neurological deficits. They further concluded that more study was needed to assess the clinical meaning of these findings. The authors indicated that this study was limited by its nonrandomized design, sample size, use of a historical control group, and baseline differences between groups. The authors also indicated that the neurological examination was simple and may have missed subtle changes in neurocognitive function. It is not clear if similar results would be expected in larger centres that perform more procedures or to other surgeons.

Piazza et al. (2009)\textsuperscript{8} conducted a comparison of 30-day mortality in patients with aortic stenosis undergoing TAVI (n=114) and SAVR (n=1008) using a prospective cohort design. The study included consecutive patients undergoing surgery for aortic stenosis from January 1\textsuperscript{st}, 2006 to December 31, 2008 at two centres (one in the Netherlands and one in Switzerland). Patients were excluded from this study if they had aortic regurgitation, required surgery on multiple valves, required aortic root reconstruction, had contraindications to TAVI or SAVR (sepsis, coagulopathy), life expectancy of less than one year, or contraindication to extracorporeal assistance. Further, in order to be eligible for TAVI, an interventional cardiologist and cardiac surgeon had to be in agreement that SAVR could not be performed. The CoreValve was used in this study. It was not specified which approach to valve insertion was used. A number of different statistical methods were used to adjust for baseline differences between groups. The primary endpoint of the study was 30-day mortality.

A total of 1633 patients underwent TAVI or SAVR during the study period, 1122 of whom met the inclusion criteria for the study (n=114 for TAVI and n=1008 for SAVR). Follow-up data were complete for all patients. The TAVI group was older than the SAVR group (82.8 ± 5.5 years
compared to 69.9 ± 11.4 years; p <0.001). The proportion of females (56.1% versus 41.5%; p<0.001) and the EuroSCORE (20.1 ± 13.4 versus 9.1 ± 10.2) were also higher in the TAVI group compared with the SAVR group. At the 30 day follow-up, 9.6% of patients in the TAVI group had died, compared to 2.3% of the SAVR group. The unadjusted OR for 30-day mortality was 4.57 (95% CI: 2.17 to 9.65). The adjusted OR ranged from 0.60 (95% CI: 0.11 to 3.36) to 7.57 (95% CI: 0.91 to 63.0). The authors concluded that both measured and unmeasured confounding factors limited their ability to draw conclusions about the mortality rate in TAVI versus SAVR and that their data suggested that TAVI could be associated with either substantial benefits or harms. They further concluded that randomized trials comparing TAVI to SAVR in aortic stenosis were needed.

The lack of randomization and baseline differences between groups are limitations to this study. The authors stated that the small number of patients undergoing TAVI and the small number of events limited their statistical analysis in that it made it difficult to adjust for differences in the two groups statistically and made the estimates imprecise (hence the large confidence intervals). It is not clear if these results would be generalizable to the Canadian population with aortic stenosis, to other surgeons with varying levels of expertise, or to a different valve such as the Edwards Sapien.

Limitations

This update to a previous report did not produce any additional information on the clinical effectiveness of percutaneous pulmonary valve replacement since the previous rapid review of this topic. No additional studies of cost-effectiveness or clinical practice guidelines were identified.

For TAVI, one additional HTA report and three observational studies were identified. Two of the three studies provided additional information about specific complications associated with TAVI, acute kidney injury6 and cerebral ischemia.7 The other study provided mortality data, but only up to 30 days.8 All studies were limited by the lack of randomization and baseline differences between groups. While the studies attempted to control for confounding using statistical analyses, this approach cannot control for unknown or unmeasured confounders in the same manner that randomization would.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

This updated rapid review based on a search from December 2009 to April 2010 did not identify any evidence from randomized controlled trials of the comparative efficacy of TAVI and SAVR, which would help to better understand the clinical implications of TAVI. Because of this, any policy decisions about TAVI or other percutaneous heart valves would have to be based on observational studies that are limited by their methodology. Patients who undergo TAVI are systematically different than patients who undergo SAVR since they are those patients not eligible for SAVR. This makes it difficult to draw conclusions about the comparative efficacy of the two surgical techniques. Results from a HTA report suggest that the expected 30-day mortality rate following TAVI is 8 to 10%. Based on data from observational studies, TAVI appeared to be less likely to cause acute kidney injury than SAVR. One study suggested that TAVI could be associated with either substantial benefits or harms, relative to SAVR. A third study found that TAVI was associated with foci of restricted diffusion on MRI, but not with
neurological deficits. No conclusions about the cost-effectiveness and guidelines for use of percutaneous heart valves could be made from the identified literature. These conclusions are similar to those of the previous rapid review that concluded that the safety and efficacy of percutaneous heart valve replacement were largely unknown, due to methodological limitations of the identified literature including study design, lack of long-term clinical data, and lack of economic data.

PREPARED BY:
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


APPENDIX: Outcomes of TAVI Performed at Canadian Centres

In 2010, Rodés-Cabau et al.\(^9\) published data from six Canadian centres that performed TAVI under the Canadian compassionate clinical use program. This appears to be the same data that were included in the HTA report from the MUHC.\(^2\) The Edwards Sapien valve was used in all procedures and was inserted via the transfemoral (n=168) or transapical (n=177) approaches. A total of 345 procedures in 339 patients were performed at the six centres between January 2005 and June 2009. The predicted surgical mortality risk score (Society of Thoracic Surgeons risk score) was 9.8 ± 6.4%.

The average patient age was 81 ± 8 years and 55% of patients were female. The valve was successfully placed in 93.3% of patients. The most common reasons for failing to insert the valve were inability to cross the native aortic valve, valve embolization with no implantation of a second valve, and procedural death. Major access site complications occurred in 13% of patients and were the most commonly encountered complication.

The 30-day mortality rates (procedural, post-procedural, and cumulative 30-day) were 1.7%, 8.7%, and 10.4%, respectively. The 30-day mortality using the transfemoral approach was 9.5% and 11.3% using the transapical approach. The mortality rate was 22.1% after a median duration of follow-up of eight months. Peri-procedural sepsis, the need for hemodynamic support, pulmonary hypertension, chronic kidney disease, and chronic obstructive pulmonary disease all increased the risk of late mortality. The mortality rates of patients who had porcelain aorta (mortality rate = 18%) or frailty (mortality rate = 25%) were similar to the entire study population (mortality rate = 22.1%).

The authors concluded that TAVI using the transfemoral and transapical approaches had mortality rates that were similar to the rate that was predicted from a surgical risk. They further concluded that baseline comorbidities (such as pulmonary hypertension, chronic kidney disease, and chronic obstructive pulmonary disease) and peri-procedural factors (such as hemodynamic support and sepsis) were associated with poor outcomes and that the insertion approach (transapical versus transfemoral) was not.