



Transcatheter Aortic Valve Replacement in Severe Aortic Stenosis: A Review of Comparative Durability and Clinical Effectiveness Beyond 12 Months

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Introduction

Aortic stenosis is a pathological condition in which progressive failure of the aortic valve to open fully¹ leads to syncope, angina, heart failure, and sudden death.² Aortic stenosis is the most common type of valve disease affecting close to 3% of patients older than 75 years of age.^{1,2} If left untreated, most patients will die within five years.¹

Transcatheter aortic valve replacement (TAVR), sometimes called transcatheter aortic valve implantation (TAVI), was developed as an alternative for patients with severe aortic stenosis who require aortic valve replacement but who are not eligible for conventional surgical aortic valve replacement (SAVR).³⁻⁶ According to a 2011 report, approximately 300,000 people worldwide have been diagnosed with severe aortic stenosis and approximately one-third of them are considered to be at too high a risk for open heart surgery.⁷ Currently, the two most common approaches for TAVR are transfemoral and transapical procedures.^{8,9} There are two commercially available systems for TAVR: SAPIEN (Edwards LifeSciences Corporation, Irvine, CA, US) and CoreValve (Medtronic Inc., Minneapolis, MN, US).^{8,10}

The benefits of TAVR with up to one year follow-up were demonstrated in two randomized controlled trials (RCTs) — PARTNER cohorts A and B^{11,12} — which showed that TAVR has statistically significant clinical benefits compared with standard therapy, or SAVR, as summarized in a previous Rapid Response review.¹³ With the aim to review long-term success and complication rates of the procedure, this report provides a review of the use of TAVR at more than 12 months follow-up in patients with severe aortic stenosis compared with SAVR or standard treatment (medical therapy plus balloon aortic valvuloplasty, if needed).

Objective

The objective of the report was to answer the following research question:

What is the evidence for the long-term (> 12 months) durability and clinical effectiveness of TAVR in patients with severe aortic stenosis compared with SAVR or standard therapy?

Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomized studies. In order to capture the long-term outcome data that may appear in abstracts but are not yet published as full articles, a search for relevant conference abstracts was also performed. Regular alerts were established to update the search until March 18, 2013.

Grey literature (literature that is not commercially published) was identified by searching relevant

sections of the Grey Matters checklist (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>). Google and other Internet search engines were used to search for additional web-based materials.

Two reviewers independently screened the retrieved citations and selected trials. They selected articles for inclusion in the review based on examination of the full-text publications according to selection criteria established a priori.

A data extraction form for the clinical effectiveness review was designed a priori to document and tabulate relevant study characteristics. Data were extracted independently by reviewers, and any disagreements were resolved through discussion until consensus was reached.

The quality of the included systematic review and trials was assessed using the AMSTAR (A Measurement Tool to Assess Reviews) and Downs and Black checklists, respectively. Numerical scores were not calculated. Instead, the strengths and limitations of individual studies are summarized and presented.

Results

Study Characteristics

Five studies were included in this review: one meta-analysis¹⁴ produced in the US, three studies reporting on the randomized controlled PARTNER trial¹⁵⁻¹⁷ conducted in the US, and one non-randomized study¹⁸ conducted in Switzerland. All studies included elderly patients with severe aortic stenosis. The mean age of the patients included in the trials ranged from 81 years¹⁴ to 84 years.¹⁵ The included patients were considered to be inoperable by conventional open surgery standards, or surgery was considered to be high risk due to age and comorbidities, such as history of coronary artery disease, previous cardiac surgery, and peripheral vascular disease.

The meta-analysis¹⁴ compared TAVR — using either the Medtronic CoreValve or Edwards SAPIEN valve — with SAVR. One RCT¹⁵ compared TAVR, using the SAPIEN valve, with SAVR; a second RCT¹⁶ compared TAVR, using the SAPIEN valve, with standard, non-surgical therapy; and the third RCT reported on a subgroup of the PARTNER trial of patients experiencing neurological events, comparing TAVR using the SAPIEN valve with SAVR. The non-randomized study¹⁸ compared TAVR, using either the CoreValve or SAPIEN valve, with SAVR. None of the studies specified the type of SAPIEN valves used.

Three studies¹⁴⁻¹⁶ reported on two-year mortality, and one¹⁸ reported 30-month mortality. One study¹⁷ reported only on neurologic events. Two of the studies^{15,16} reported on neurologic events, as well as myocardial infarction, major bleeding, renal failure, new pacemaker placement, and surgical replacement.

Summary of Findings

The meta-analysis and the four studies compared the evidence for the long-term (> 12 months) durability and clinical effectiveness of TAVR in high-risk patients with severe aortic stenosis to SAVR or medical treatment (standard treatment).¹⁴⁻¹⁸ In general, at two years follow-up, TAVR was similar to SAVR in mortality rate, symptoms reduction, pacemaker implantation rate, and valve hemodynamic improvement, but major vascular complications and aortic valvular regurgitation were more common after TAVR. Compared with standard medical treatment, TAVR significantly reduced mortality rate and symptoms, and improved valve hemodynamics for up to 30 months of follow-up.

The meta-analysis compared complications and mortality between TAVR and SAVR.¹⁴ There was no difference found in TAVR and SAVR outcomes in mortality at up to two years of follow-up. This systematic review pooled data

from 29 studies with different study designs, different study sizes, and differences in patient baseline characteristics. Many patients undergoing SAVR also underwent coronary artery bypass grafting, which is a major confounding factor.

One of the studies reporting on the randomized controlled PARTNER trial on high-risk patients with aortic stenosis compared two-year outcomes between patients undergoing TAVR with the Edwards SAPIEN valve with SAVR.¹⁵ There were no statistically significant differences between the two methods in mortality, repeat hospitalization, neurologic events, myocardial infarction, endocarditis, renal failure, and new pacemaker placement. Echocardiographic findings showed that both methods provided similar improvements in hemodynamics, such as valve areas and mean gradients, but moderate and severe paravalvular aortic regurgitation occurred more frequently after TAVR; the presence of regurgitation was associated with increased late mortality.

Another analysis of the PARTNER trial compared two-year outcomes between patients undergoing TAVR with the Edwards SAPIEN valve to standard therapy.¹⁶ TAVR was found to be statistically significantly superior to standard therapy for most study outcomes such as mortality, rehospitalization, stroke, balloon valvuloplasty, and New York Heart Association (NYHA) functional class III or IV frequencies. Echocardiographic findings showed that both methods had a similar aortic regurgitation rate at two years.

Neurological event risks for patients from the PARTNER trial were reported, in the third study, for patients undergoing TAVR and SAVR.¹⁷ There

was an early peak of neurologic events in both groups within the first week after treatment, with a higher risk after TAVR compared with SAVR. The risk of neurologic events declined to a constant hazard phase in both groups at up to two years of follow-up, which may be associated with patient and disease-related factors, such as advanced functional impairment (NYHA functional classification) and recent history of stroke.

The clinical outcomes in patients undergoing TAVR, SAVR, or medical therapy were compared in the non-randomized, prospective observational study.¹⁸ Long-term clinical outcomes at up to 30 months of follow-up reconfirmed the similarity between TAVR and SAVR groups, and the superiority of TAVR compared with the medical treatment groups, in all-cause or cardiovascular death, composite end point all-cause death/major stroke, or all-cause death/major stroke/myocardial infarction.

Limitations

The robustness of the evidence on the comparative long-term clinical efficacy of TAVR is limited because of the nature of the available evidence. The included meta-analysis¹⁴ pooled data from studies with different designs, sample sizes, and baseline characteristics, reducing the strength of direct comparisons. All three RCTs included in the review were from one trial (PARTNER); patients were randomized, but in the included studies, most study sites were reporting on their initial experiences with TAVR, resulting in a potential learning curve impact on the results as surgeons gained experience with the technique. Patient enrollment into the non-randomized study might have influenced an investigator's decision to attempt treatment.

Conclusions

Long-term outcomes support the use of TAVR as an alternative to SAVR in selected high-risk patients with aortic stenosis. The two methods yielded similar clinical outcomes and hemodynamic findings. Major vascular complications and neurologic events were more frequent with TAVR. Compared with standard treatment, TAVR reduced the rates of mortality, hospitalization, and strokes, and it improved symptoms based on NYHA classification.

An Ontario report in 2012 systematically reviewed the safety and effectiveness of TAVR compared with SAVR and standard treatment.¹⁹ The report found that TAVR and SAVR had similar mortality rates at one year, and the TAVR group showed higher rates of major vascular complications and neurologic events. This review found that the clinical benefits and complications of TAVR reported in the Ontario report were maintained to at least two years.

Despite the demonstrated benefits of TAVR, the increased frequency of adverse events following the procedure remains a significant hurdle. A recent multi-centre Canadian study examined the long-term outcomes of TAVR in inoperable and high-risk patients (there was no comparison with SAVR or other medical therapies in this study).²⁰ The study found that, at a mean follow-up of 42 ± 15 months, more than one-half of the patients had died (59% of which were from non-cardiac causes), and there was no clinically significant deterioration in valve function. It is noteworthy that the poor outcomes in this study may reflect the severe conditions of the population under study.

The benefits and risks of TAVR need to be further elucidated with studies that include surgeons with more experience with the procedure and that incorporate later generation devices. Careful patient selection, methodical risk stratification, optimal valve sizing, and thorough procedural techniques,

together with comprehensive complications management, are important factors to consider for achieving good outcomes.

References

1. Van Brabant H, Neyt M, Hulstaert F. Transcatheter aortic valve implantation (TAVI): risky and costly. *BMJ* [Internet]. 2012 Jul 31 [cited 2013 Mar 6];345:e4710. Available from: <http://www.bmj.com/content/345/bmj.e4710>
2. Chu MW, Borger MA, Mohr FW, Walther T. Transcatheter heart-valve replacement: update. *CMAJ* [Internet]. 2010 May 18 [cited 2013 Mar 6];182(8):791-5. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2871201>
3. Jilaihawi H, Doumanian A, Stegic J, Fontana G, Makkar R. Transcatheter aortic valve implantation: patient selection and procedural considerations. *Future Cardiol*. 2011 Jul;7(4):499-509.
4. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *Eur Heart J* [Internet]. 2011 Jan [cited 2013 Jun 12];32(2):205-17. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021388>
5. Kempfert J, Lehmann S, Linke A, Rastan A, Van Linden A, Blumenstein J, et al. Latest advances in transcatheter aortic valve implantation. *Surg Technol Int*. 2010;19:147-54.
6. Cribier A. Development of transcatheter aortic valve implantation (TAVI): a 20-year odyssey. *Arch Cardiovasc Dis*. 2012 Mar;105(3):146-52.
7. The Healthcare Sales & Marketing Network [Internet]. Newtown Square (PA): Healthcare Sales & Marketing Network, LLC; 2011. Study shows Medtronic CoreValve(R) system efficacy and durability through four years in longest-term industry data available; 2011 Aug 28 [cited 2013 Jun 12]. Available from: http://salesandmarketingnetwork.com/news_release.php?ID=2033759

8. Salinas P, Moreno R, Lopez-Sendon JL. Transcatheter aortic valve implantation: current status and future perspectives. *World J Cardiol* [Internet]. 2011 Jun 26 [cited 2013 Jan 23];3(6):177-85. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139039>
9. Mack MJ. Access for transcatheter aortic valve replacement: which is the preferred route? *JACC Cardiovasc Interv*. 2012 May;5(5):487-8.
10. Neragi-Miandoab S, Skripochnik E, Michler RE. Recently patented and widely used valves for transcatheter aortic valve implantation. *Recent Pat Cardiovasc Drug Discov*. 2012;7(3):196-205.
11. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* [Internet]. 2010 Oct 21 [cited 2013 Jun 12];363(17):1597-607. Available from: <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1008232>
12. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* [Internet]. 2011 Jun 9 [cited 2013 Mar 23];364(23):2187-98. Available from: <http://www.nejm.org/doi/full/10.1056/NEJMoa1103510>
13. Canadian Agency for Drugs and Technologies in Health. Transcatheter aortic valve implantation for aortic stenosis: a review of the clinical effectiveness and guidelines [Internet]. Ottawa: CADTH; 2011 Oct 28. (Rapid response report: summary with critical appraisal). [cited 2013 Mar 6]. Available from: <http://www.cadth.ca/media/pdf/htis/oct-2011/RC0303-000%20Tavi%20final.pdf>
14. Jilaihawi H, Chakravarty T, Weiss RE, Fontana GP, Forrester J, Makkar RR. Meta-analysis of complications in aortic valve replacement: comparison of Medtronic-Corevalve, Edwards-Sapien and surgical aortic valve replacement in 8,536 patients. *Catheter Cardiovasc Interv*. 2012 Jul 1;80(1):128-38.
15. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012 May 3;366(18):1686-95.
16. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med*. 2012 May 3;366(18):1696-704.
17. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg*. 2012 Apr;143(4):832-43.
18. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol*. 2011 Nov 15;58(21):2151-62.
19. Sehatzadeh S, Doble B, Xie F, Blackhouse G, Campbell K, Kaulback K, et al. Transcatheter Aortic Valve Implantation (TAVI) for treatment of aortic valve stenosis: an evidence-based analysis (Part B). *Ont Health Technol Assess Ser* [Internet]. 2012 May [cited 2013 Jun 4];12(14):1-62. Available from: http://www.hqontario.ca/en/eds/tech/pdfs/2012/rev_TAVI_May.pdf
20. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Osten M, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. *J Am Coll Cardiol*. 2012 Nov 6;60(19):1864-75.

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