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Peer-Reviewed Summary with Critical Appraisal

CADTH

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

April 2013

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

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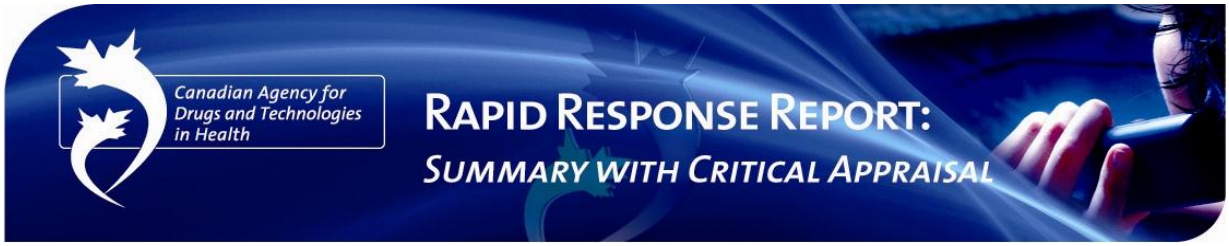
April 2013



Health technology assessment agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision-making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Rapid Response Service provides Canadian health care decision-makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by Rapid Response Service is tailored to meet the needs of decision-makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this Rapid Response assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

This report is a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") that are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of reviewers.

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The following individuals kindly provided comments on this report.

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Conflicts of Interest

Dr. Marc Ruel received a grant from Medtronic (Proctor).

Manufacturers were provided with an opportunity to comment on an earlier version of this report. All comments that were received were considered when preparing the final report.

TABLE OF CONTENTS

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

DATE: April 2013

EXECUTIVE SUMMARY

Context and Policy Issues

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). 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 too high risk for open heart surgery. Currently, the two most common approaches for TAVR are transfemoral and transapical procedures. There are two commercially available systems for TAVR: Edwards Sapien (LifeSciences, Irvine, CA, US) and CoreValve (Medtronic, Minneapolis, MN, US).

The benefits of TAVR with up to one year follow-up were demonstrated in two randomized controlled trials (RCTs) — PARTNER cohorts A and B — which showed that TAVR has statistically significant clinical benefits compared with standard therapy or SAVR, as summarized in a previous Rapid Response review. With the aim to review long-term success and complication rates of the procedure, this report will provide 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).

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

A peer-reviewed literature search was conducted using the following bibliographic databases: PubMed, MEDLINE, Embase, The Cochrane Library (2012, Issue 11), and the University of York Centre for Reviews and Dissemination (CRD) databases. Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/index.php/en/cadth/products/grey-matters). Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and November 23, 2012. Regular alerts were established to update the search until March 18, 2013. Two independent reviewers screened articles using predefined criteria.

Summary of Findings

One meta-analysis and 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). In general, at two years follow-up, TAVR was similar to SAVR with respect to 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 in up to 30 months follow-up.

The robustness of the evidence on the comparative long-term clinical efficacy of TAVR is limited, due to the nature of the available evidence. The included meta-analysis 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 this was the initial experience with TAVR at most sites, 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 impacted an investigator's decision to attempt treatment.

Conclusions and Implications for Decision or Policy-Making

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 improved symptoms. Despite the demonstrated benefits of TAVR, the increased frequency of adverse events following TAVR remains a significant challenge. Cautious patient selection, methodical risk stratification, optimal valve sizing, and thorough procedural techniques with surgeons past the learning curve, together with comprehensive complications management are important factors to achieve good outcomes.

1 CONTEXT AND POLICY ISSUES

Aortic stenosis is a pathological condition in which progressive failure of the aortic valve to open fully[1] 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.[1,2] If left untreated, most patients will die within five years.[1] As Canada currently counts 2,068,670 persons older than 75 years,[3] the estimated number of Canadians with aortic stenosis is 62,060.

The TAVR procedure, sometimes called TAVI, was developed as an alternative for patients with severe aortic stenosis who require aortic valve replacement but who are not eligible for conventional SAVR.[4-7] According to a 2011 report, approximately 300,000 people worldwide have been diagnosed with this condition, and approximately one-third of them are considered too high risk (patients with coexisting conditions that were associated with an increased risk of death of 15% or higher by 30 days after surgery) for open heart surgery.[8] As a result TAVR may be an alternative for about 20,000 persons in Canada.

Currently, the two most common approaches for TAVR are transfemoral and transapical procedures.[9,10] There are two commercially available systems for TAVR: Edwards Sapien (LifeSciences, Irvine, CA, US) and CoreValve (Medtronic, Minneapolis, MN, US).[9,11] The Edwards Sapien system was approved for use by Health Canada in 2011 for the transfemoral approach,[12] and the CoreValve system is available in Canada through the Special Access Programme.[8] A number of next generation valves for TAVR have been developed and are in early clinical evaluation, such as the Lotus valve (Boston Scientific Inc., Natick, Massachusetts), the Direct Flow valve (Direct Flow Medical Inc., Santa Rosa, California), Jena valve (JenaValve, Munich, Germany), Engager valve (Medtronic Inc., Minneapolis, MN, US), Portico valve (St. Jude Medical, St. Paul, MN, US), and the Symetis Acurate valve (Symetis SA, Ecublens, Switzerland).[13,14]

Benefits of TAVR with up to one year follow-up were demonstrated in two RCTs (PARTNER cohorts A and B),[15,16] which showed that TAVR has statistically significant clinical benefits compared with standard therapy (medical therapy plus balloon aortic valvuloplasty if needed) in inoperable patients or conventional SAVR in high-risk surgical patients, as summarized in a previous Rapid Response review.[17] To evaluate long-term success and complication rates of the procedure, this report will provide 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 medical treatment.

2 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?

3 KEY FINDINGS

In follow-up longer than 12 months, findings support the use of TAVR as an alternative to conventional surgery in selected high-risk patients with aortic stenosis, with similar clinical outcomes such as mortality and rehospitalization rates, neurologic events, and myocardial infarction. Major vascular complications and neurologic events were more frequent with TAVR. The two methods, TAVR and SAVR, had similar echocardiographic hemodynamic findings. Compared with standard treatment, TAVR was superior with regard to long-term clinical outcomes and improved symptoms. A meta-analysis of larger trials with sensitivity analyses on study design, sample size, baseline characteristics, and surgeon's experience is needed to reconfirm the findings.

4 METHODS

4.1 Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with in-process records & daily updates through Ovid; Embase through Ovid; The Cochrane Library (2012, Issue 11) through Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts were TAVR and patients with aortic stenosis.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and November 23, 2012. Regular alerts were established to update the search until March 18, 2013. See Appendix 1 for the detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). Google and other Internet search engines were used to search for additional web-based materials. See Appendix 1 for more information on the grey literature search strategy.

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.

4.2 Selection Criteria and Methods

Two reviewers (CH and KC) independently screened citations and selected trials relevant to the research question regarding TAVR in severe aortic stenosis. The decision to order an article in full text for closer examination was based on screening of the title of each citation and its abstract, when available. In cases of insufficient information, the article was ordered for further information. Two reviewers (CH and KC) selected the final articles for inclusion based on examination of the full-text publications. A study was included for review according to selection criteria established a priori (Table 1). Any disagreement between reviewers was discussed until consensus was reached. The trial selection process is presented in a flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix 2).[18]

4.3 Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they did not have a comparator group, if they were published before January 2007, if they were duplicate publications of the same study, or if they were referenced in the selected systematic review. A study inclusion / exclusion form for the clinical effectiveness review was designed a priori, and is shown in Appendix 3.

4.4 Data Extraction Strategy

A data extraction form for the clinical effectiveness review was designed a priori to document and tabulate relevant study characteristics, and is provided in Appendix 4. Data were extracted independently by reviewers (CH and KC), and any disagreements were resolved through discussion until consensus was reached.

Table 1: Selection Criteria	
Population	Patients with severe aortic stenosis
Intervention	TAVR Valves include, but are not limited to: Edwards Sapien THV (Model 9000 TFX) valve Edwards Sapien XT transcatheter heart valve Medtronic CoreValve System
Comparator	SAVR Standard medical therapy
Outcomes	At > 12 months: Condition-related outcomes including heart failure symptoms, dyspnea on exertion, ability to walk, mortality, time to death, change in New York Heart Association (NYHA) heart failure class, angina (chest pain), and quality of life Procedure-related outcomes including mortality, quality of life, bleeding, major adverse cardiovascular events (MACE) (e.g., myocardial infarction, stroke, etc.), repeat hospitalization, valve durability/structural valve deterioration/need for replacing the valve (either through repeat TAVR or SAVR), valvular or paravalvular regurgitation, and other adverse events or complications reported in trials (e.g., need for pacemaker insertion, endocarditis, renal failure) Valve hemodynamics/echocardiographic findings including valve areas, valve mean pressure gradient, and paravalvular regurgitation
Study design	Health technology assessments, systematic reviews, meta-analyses, RCTs and non-RCTs

RCT = randomized controlled trial; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

4.5 Critical Appraisal of Individual Studies

The quality of the included systematic review and trials was assessed using the AMSTAR[19] and Downs and Black checklists[20] respectively. Numerical scores were not calculated. Instead, the strengths and limitations of individual studies are summarized and presented.

5 SUMMARY OF EVIDENCE

5.1 Quantity of Available Evidence

The literature search yielded 874 citations. Two additional studies were identified by searching the grey literature. After screening the abstracts, 31 potentially relevant studies were selected for full-text review. Five studies were included in the review. Included and excluded trials are listed in Appendices 5 and 6 respectively.

The PRISMA flowchart in Appendix 2 details the process of the study selection.

5.2 Summary of Study Characteristics

A detailed summary of the included studies' characteristics is provided in Appendix 7.

5.2.1 Study design

Five studies are included in this review: one meta-analysis[21] produced in the US, three studies reporting on the randomized controlled PARTNER trial[22-24] conducted in the US, and one non-randomized study[25] conducted in Switzerland.

5.2.2 Population

All studies included elderly patients with severe aortic stenosis. The mean age of the patients included in the trials ranged from 81 years[21] to 84 years.[22] 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.

5.2.3 Interventions and comparators

The meta-analysis[21] compared TAVR, using either the Medtronic CoreValve or Edwards Sapien valve, with SAVR. One RCT[22] compared TAVR, using the Sapien valve, with SAVR; a second RCT[23] 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 study[25] compared TAVR, using either the CoreValve or Sapien valve, with SAVR. None of the studies specified the type of Sapien valves used.

5.2.4 Outcomes

Three studies[21-23] reported on two-year mortality, and one[25] reported 30-month mortality. One study[24] reported only on neurologic events. Two of the studies[22,23] reported on neurologic events, as well as myocardial infarction, major bleeding, renal failure, new pacemaker placement, and surgical replacement.

5.3 Summary of Critical Appraisal

A detailed summary of the included studies' critical appraisal is provided in Appendix 8. The meta-analysis included in the report[21] was based on a comprehensive literature search, but pooled data from trials with different designs on patients with different baseline characteristics, affected the certainty of the pooled findings. The scientific quality of the studies included in the meta-analysis was not documented, and it was unclear whether publication bias was assessed. The included RCTs[22-24] that were from the same PARTNER trial, did not blind patients to the intervention they received, and did not report clearly on patients lost to follow-up, creating potential differences between intention-to-treat and as-treated cohorts. These studies were sufficiently powered to detect clinically important effects. Because no power calculation was provided, it was not clear if the non-randomized study had an adequate sample size to detect clinically important effects.[25] The included studies were from the early experiences of the surgeons with TAVR, as this was the initial experience with TAVR at most sites. As such, they may not be representative of outcomes past the learning curve, when outcomes may be expected to improve due to increased experience with the technique.

5.4 Summary of Findings

Main findings of included studies are summarized in detail in Appendix 9.

One meta-analysis and four studies compared the evidence for the long-term (> 12 months) durability and clinical effectiveness of TAVR in patients with severe aortic stenosis to SAVR or medical treatment (standard treatment).[21-25] In general, at two-years follow-up, TAVR was similar to SAVR with respect to mortality rate, symptoms reduction, and valve hemodynamics improvement, but major vascular complications and aortic valvular regurgitation were more

common after TAVR. Compared with medical treatment, TAVR significantly reduced mortality rates and symptoms, and improved valve hemodynamics in up to 30-months follow-up.

A meta-analysis on elderly and high-risk patients with aortic stenosis undergoing TAVR with Medtronic CoreValve or Edwards Sapien valve (n = 5,024), or SAVR (n = 3,512), compared complications and mortality between the two techniques.[21] There was no difference found in TAVR and SAVR outcomes in mortality at up to two years 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.

An analysis from the randomized controlled PARTNER trial on high-risk patients with aortic stenosis compared two-year outcomes between patients undergoing TAVR with Edwards Sapien valve (n = 348) to SAVR (n = 351).[22] There were no statistically significant differences between the two methods in terms of 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.

An analysis from the PARTNER trial on high-risk patients with aortic stenosis compared two-year outcomes between patients undergoing TAVR with Edwards Sapien valve (n = 179) to standard therapy (n = 179).[23] TAVR was found to be statistically significantly superior to standard therapy with regard to most study outcomes such as mortality, rehospitalization, stroke, balloon valvuloplasty, and NYHA 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 another publication for patients undergoing TAVR (n = 344) and SAVR (n = 313).[24] 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 class) and recent history of stroke.

The clinical outcomes in patients undergoing TAVR (n = 257), SAVR (n = 107), or medical therapy (n = 78) were compared in a prospective observational study.[25] Long-term clinical outcomes up to 30-months follow-up reconfirmed the similarity between TAVR and SAVR groups, and the superiority of TAVR compared to the medical treatment groups, with regard to all-cause or cardiovascular death, composite end point all-cause death / major stroke, or all-cause death / major stroke / myocardial infarction.

In an attempt to capture data on long-term outcomes of TAVR that were not yet published as full articles, a brief summary and list of relevant conference abstracts is presented in Appendix 10.

5.5 Limitations

The robustness of the evidence on the comparative long-term clinical efficacy of TAVR is limited, due to the nature of the available evidence. The included meta-analysis pooled data from studies with different designs, sample sizes, and baseline characteristics, reducing the appropriateness of pooling data. All three RCTs included in the review were from one trial (PARTNER); patients were randomized, but most surgeons had only early experience with TAVR, resulting in a learning curve impact on the results. Patient enrollment into the non-randomized study might have impacted an investigator's decision to attempt treatment.

6 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY-MAKING

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 class. These clinical outcomes were further confirmed in the attached report of conference abstracts (Appendix 10). The abstracts also demonstrated that both the Medtronic CoreValve and Edwards Sapien valves may have successful long-term durability at three, four, and five years. Emerging findings from the three-year follow-up data from the PARTNER A trial, not available during the production of this report, will help to elucidate the benefits and harms following TAVR in patients with severe aortic stenosis.

An Ontario report in 2012 systematically reviewed the safety and effectiveness of TAVR compared with SAVR and standard treatment.[26] 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 Rapid Response 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 TAVR remains a significant hurdle. A recent multicentre Canadian study examined the long-term outcomes of TAVR in inoperable and high-risk patients (there was no comparison to SAVR or other medical therapy in this study).[27] 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 elucidated with more studies using surgeons past the learning curve, and incorporating 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.

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23. 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.

24. 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.

25. 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.

26. 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 2012 Dec 4];12(14):1-62. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377530/pdf/ohtas-12-62.pdf

27. 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.

APPENDIX 1: LITERATURE SEARCH STRATEGY

Overview	
Interface:	Ovid
Databases:	Embase Ovid MEDLINE In-Process & Other Non-Indexed Citations Ovid MEDLINE Daily Ovid MEDLINE 1946 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 21, 2012
Alerts:	Monthly search updates began November 21, 2012 and ran until March 18, 2013.
Study Types:	Systematic reviews; meta-analyses; technology assessments; RCTs; controlled clinical trials; multicentre studies; cohort studies; cross-over studies; case control studies; comparative studies; epidemiologic studies.
Limits:	Publication years January 1, 2007 to November 21, 2012 Humans English
Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type

Multi-Database Strategy	
1	(Aortic valve/ or Heart Valve Prosthesis Implantation/ or Heart valve prosthesis/ or *Bioprosthesis/ or bioprosthes*.ti,ab.) and (exp Heart Catheterization/ or (Transcutaneous or transcatheter or percutaneous).ti,ab.) and (implantation or prosthesis or prostheses or replacement or revalving or revalve or repair*).ti,ab.
2	((Transcutaneous or transcatheter or percutaneous) adj3 (aortic or cardiac or heart or sapien or edwards) adj3 valve*).ti,ab.
3	(PARTNER* or SAPIEN or CoreValve or TAVI or TAVR or PAVR).ti,ab.
4	1 or 2 or 3
5	exp Aortic Valve Stenosis/ or ((aortic adj3 stenosis) or (aortic adj3 stenoses)).ti,ab.
6	4 and 5
7	6 use pmez
8	(aorta valve/ or aorta valve replacement/ or aorta valve prosthesis/ or exp heart valve bioprosthesis/ or bioprosthes*.ti,ab.) and (heart catheterization/ or (transcatheter or percutaneous).ti,ab.) and (implantation or prosthesis or prostheses or replacement or revalving or revalve).ti,ab.
9	((transcatheter or percutaneous) adj3 (aortic or cardiac or heart or sapien or edwards) adj3 valve*).ti,ab.
10	(PARTNER* or SAPIEN or CoreValve or TAVI or TAVR or PAVR).ti,ab.
11	transcatheter aortic valve implantation/
12	8 or 9 or 10 or 11
13	aorta valve stenosis/ or ((aortic adj3 stenosis) or (aortic adj3 stenoses)).ti,ab.
14	12 and 13
15	14 not conference abstract.pt.
16	15 use oemezd
17	7 or 16
18	meta-analysis.pt.
19	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
20	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
21	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
22	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
23	(data synthes* or data extraction* or data abstraction*).ti,ab.
24	(handsearch* or hand search*).ti,ab.
25	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
26	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview*).ti,ab.
27	(meta regression* or metaregression*).ti,ab.
28	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
29	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
30	(cochrane or (health adj2 technology assessment) or evidence report).jw.
31	(meta-analysis or systematic review).md.
32	(comparative adj3 (efficacy or effectiveness)).ti,ab.
33	(outcomes research or relative effectiveness).ti,ab.
34	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
35	or/18-34

Multi-Database Strategy	
36	Randomized Controlled Trial.pt.
37	Randomized Controlled Trials as Topic/
38	"Randomized Controlled Trial (topic)"/
39	Randomized Controlled Trial/
40	Randomization/
41	Random Allocation/
42	Double-Blind Method/
43	Double Blind Procedure/
44	Double-Blind Studies/
45	Single-Blind Method/
46	Single Blind Procedure/
47	Single-Blind Studies/
48	Placebos/
49	Placebo/
50	(random* or sham or placebo*).ti,ab,hw.
51	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
52	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
53	or/36-52
54	epidemiologic methods.sh.
55	epidemiologic studies.sh.
56	cohort studies/
57	cohort analysis/
58	longitudinal studies/
59	longitudinal study/
60	prospective studies/
61	prospective study/
62	follow-up studies/
63	follow up/
64	followup studies/
65	retrospective studies/
66	retrospective study/
67	case-control studies/
68	exp case control study/
69	cross-sectional study/
70	observational study/
71	quasi experimental methods/
72	quasi experimental study/
73	validation studies.pt.
74	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
75	(cohort adj7 (study or studies or design or analysis or analyses)).ti,ab.
76	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
77	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
78	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
79	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
80	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
81	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
82	(population adj3 (study or studies or analysis or analyses)).ti,ab.

Multi-Database Strategy	
83	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
84	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
85	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
86	((natural adj experiment) or (natural adj experiments)).ti,ab.
87	(quasi adj (experiment or experiments or experimental)).ti,ab.
88	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
89	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
90	case series.ti,ab.
91	case reports.pt.
92	case report/
93	case study/
94	(case adj3 (report or reports or study or studies or histories)).ti,ab.
95	organizational case studies.sh.
96	or/54-95
97	35 or 53 or 96
98	17 and 97
99	(comment or newspaper article or editorial or letter or note).pt.
100	98 not 99
101	remove duplicates from 100
102	limit 101 to english language
103	limit 102 to yr="2007 -Current"

Other Databases	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 11, 2012	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

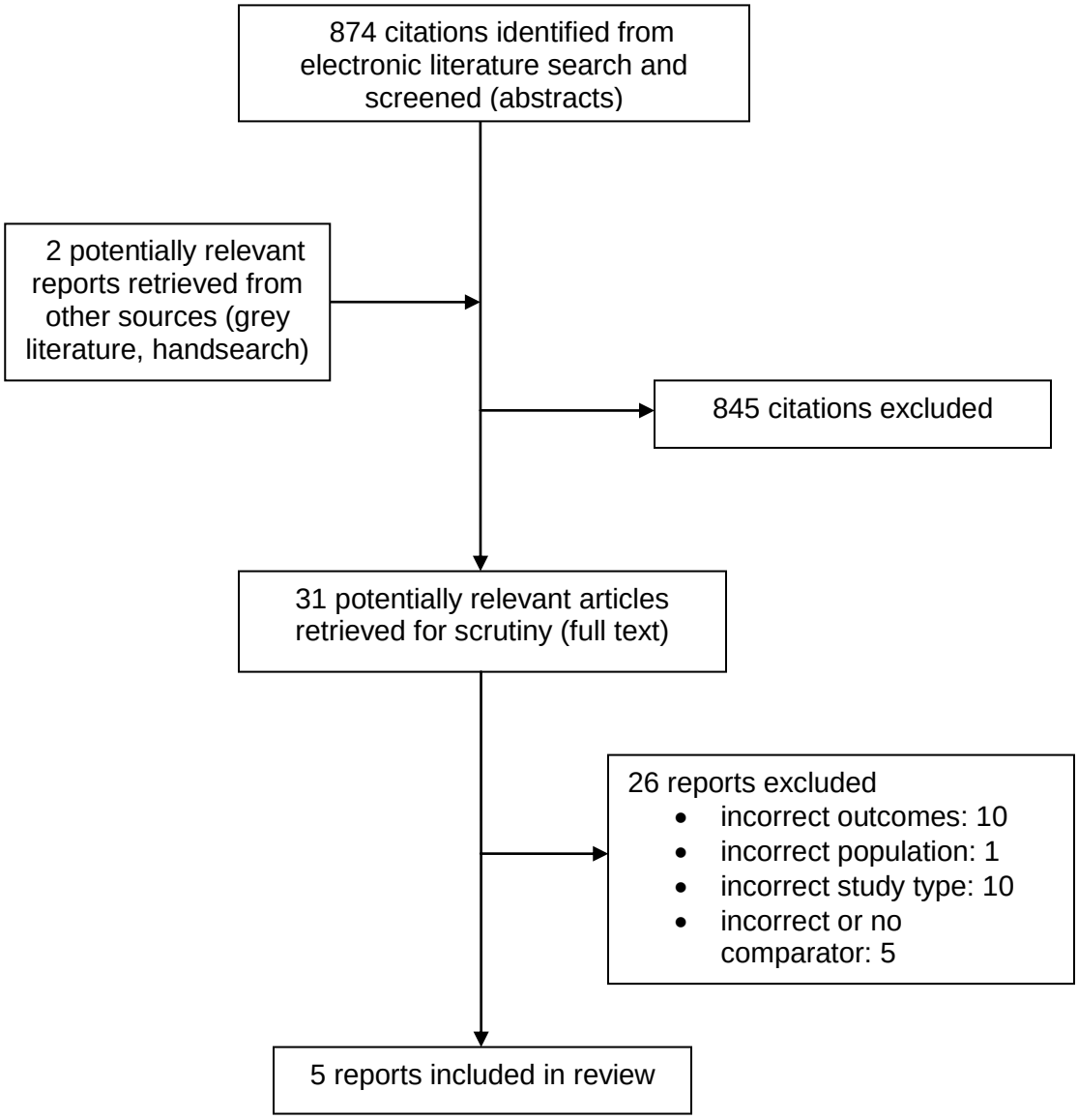
Grey Literature	
Dates for Search:	November 22, 23, 26 2012
Keywords:	Included terms for transcatheter aortic valve implantation, aorta valve stenosis.
Limits:	Publication years 2007-present Humans English

The following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/resources/grey-matters) were searched:

- Advisories & Warnings
- Background
- Clinical Trial Listing
- Databases (free)
- Health Technology Assessment Agencies
- Internet Search
- Open Access Journals
- Regulatory Approvals.

Conferences and Meetings	
Database: Dates for Search:	Embase November 27, 2012
Strategy:	Same MeSH, keywords, and date limits used as per Embase search, excluding study types (see Multi-Database Strategy above).
Limits:	Publication years 2011-present Humans English

APPENDIX 2: SELECTION OF PUBLICATIONS



APPENDIX 3: CLINICAL STUDY INCLUSION / EXCLUSION FORM

Transcutaneous Aortic Valve Replacement in Severe Aortic Stenosis: A Review of Long-Term Durability and Clinical Effectiveness

Title:
First author and year:

Reviewer:

INCLUSION CRITERIA:

1. Population: yes_____ no_____ can't tell_____
- Patients with severe aortic valve stenosis

2. Intervention: yes_____ no_____ can't tell_____
- TAVR

3. Comparator: yes_____ no_____ can't tell_____
- SAVR
- Medical therapy

4. Outcome Measures (any of): yes_____ no_____ can't tell_____
- Condition-related outcomes including heart failure symptoms, dyspnea on exertion, ability to walk, mortality, time to death, change in NYHA heart failure class, angina (chest pain), quality of life.
- Procedure-related outcomes including mortality, quality of life, bleeding, MACE (e.g., myocardial infarction, stroke, etc.), repeat hospitalization, valve durability / structural valve deterioration / need for replacing the valve (either through repeat TAVR or SAVR), valvular / paravalvular regurgitation, other adverse events / complications reported in trials (e.g., need for pacemaker insertion, or occurrence of endocarditis, renal failure).
- Valve hemodynamics / echocardiographic findings: valve areas, valve mean pressure gradient, paravalvular regurgitation.

5. Study Design: yes_____ no_____ can't tell_____
- Systematic review / meta-analysis, RCTs, non-randomized studies.
- **"yes" (1 to 5 inclusive): include study and order full paper**_____
- **at least one "can't tell" and others "yes" for 1 to 5: order full paper for further review** _____
- **"no" (any 1 to 5): exclude study.**

APPENDIX 4: CLINICAL STUDY DATA EXTRACTION FORM

Long-term (> 12 months) Clinical Evidence and Durability of TAVR in Severe Aortic Stenosis

Reviewer: *C. Ho*_____ *K. Cimon* _____

Study title:		
Author:		
ID #: Year:		
Methods		
Study design		
Study duration		
Population - Number of patients randomized or selected - Number of patients completing the study		
Diagnosis		
Eligibility criteria		
Country of origin		
Industry sponsorship	☐ Yes ☐ No ☐ Unknown	
Baseline Characteristics of Study Participants		
- Age - Diagnosis - Others		
Outcomes	**Intervention**	**Comparator**

CLINICAL OUTCOMES
at > 12 months follow-up
• Death
  ○ from any cause
  ○ from cardiovascular causes
• Repeat hospitalization
• Neurologic events (Stroke or TIA)
• Myocardial infarction
• Major vascular complications
• Major bleeding
• Endocarditis
• Renal failure
• New pacemaker		

DURABILITY at > 12 months follow-up • SVD requiring surgical replacement • Echocardiographic findings (valve areas, mean gradients, valvular regurgitation…)		
Comments		

SVD = structural valve deterioration; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

APPENDIX 5: INCLUDED TRIALS FOR CLINICAL EVIDENCE

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.

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.

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.

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.

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

APPENDIX 6: EXCLUDED TRIALS FOR CLINICAL EVIDENCE

Incorrect outcomes (not greater than 12 months)

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 2012 Dec 4];363(17):1597-607. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1008232

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 [cited 2012 Dec 4];12(14):1-62. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377530/pdf/ohtas-12-62.pdf

Nuis RJ, Dager AE, van der Boon RM, Jaimes MC, Caicedo B, Fonseca J, et al. Patients with aortic stenosis referred for TAVI: treatment decision, in-hospital outcome and determinants of survival. Neth Heart J [Internet]. 2012 Jan [cited 2013 Mar 20];20(1):16-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3247629/pdf/12471_2011_Article_224.pdf

Fusari M, Bona V, Muratori M, Salvi L, Salis S, Tamborini G, et al. Transcatheter vs. surgical aortic valve replacement: a retrospective analysis assessing clinical effectiveness and safety. J Cardiovasc Med (Hagerstown). 2012 Apr;13(4):229-41.

Reynolds MR, Magnuson EA, Wang K, Lei Y, Vilain K, Walczak J, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation [Internet]. 2012 Mar 6 [cited 2012 Dec 4];125(9):1102-9. Available from: http://circ.ahajournals.org/content/125/9/1102.full.pdf+html

Ben-Dor I, Pichard AD, Gonzalez MA, Weissman G, Li Y, Goldstein SA, et al. Correlates and causes of death in patients with severe symptomatic aortic stenosis who are not eligible to participate in a clinical trial of transcatheter aortic valve implantation. Circulation [Internet]. 2010 Sep 14 [cited 2012 Dec 5];122(11 Suppl):S37-S42. Available from: http://circ.ahajournals.org/content/122/11_suppl_1/S37.full.pdf+html

Osnabrugge RL, Head SJ, Genders TS, van Mieghem NM, de Jaegere PP, van der Boon RM, et al. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. Ann Thorac Surg. 2012 Sep 6;94(1954):1960.

Incorrect outcomes or data unusable as presented

Ewe SH, Ajmone MN, Pepi M, Delgado V, Tamborini G, Muratori M, et al. Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis. Am Heart J. 2010 Dec;160(6):1113-20.

Ben-Dor I, Dvir D, Barbash IM, Okubagzi P, Torguson R, Xue Z, et al. Outcomes of patients with severe aortic stenosis at high surgical risk evaluated in a trial of transcatheter aortic valve implantation. Am J Cardiol. 2012 Oct 1;110(7):1008-14.

Pilgrim T, Wenaweser P, Meuli F, Huber C, Stortecky S, Seiler C, et al. Clinical outcome of high-risk patients with severe aortic stenosis and reduced left ventricular ejection fraction undergoing medical treatment or TAVI. PLoS ONE [Internet]. 2011 [cited 2012 Dec 4];6(11):e27556, 2011. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3213147/pdf/pone.0027556.pdf

Incorrect population

Chitsaz S, Jaussaud N, Chau E, Yan KS, Azadani AN, Ratcliffe MB, et al. Operative risks and survival in veterans with severe aortic stenosis: surgery versus medical therapy. Ann Thorac Surg. 2011 Sep;92(3):866-72.

Incorrect study type

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.

Genereux P, Head SJ, Wood DA, Kodali SK, Williams MR, Paradis JM, et al. Transcatheter aortic valve implantation 10-year anniversary: review of current evidence and clinical implications. Eur Heart J. 2012 Oct;33(19):2388-98.

Bourantas CV, Farooq V, Onuma Y, Piazza N, van Mieghem NM, Serruys PW. Transcatheter aortic valve implantation: new developments and upcoming clinical trials. EuroIntervention. 2012 Sep 20;8(5):617-27.

Forrest JK. Transcatheter aortic valve replacement: design, clinical application, and future challenges. Yale J Biol Med. 2012 Jun [cited 2013 Mar 20];85 (2):239-47. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3375667

Webb JG, Wood DA. Current status of transcatheter aortic valve replacement. J Am Coll Cardiol. 2012 Aug 7;60(6):483-92.

Cribier A. Development of transcatheter aortic valve implantation (TAVI): a 20-year odyssey. Arch Cardiovasc Dis. 2012 Mar;105(3):146-52.

Ruiz CE, Laborde JC, Condado JF, Chiam PT, Condado JA. First percutaneous transcatheter aortic valve-in-valve implant with three year follow-up. Catheter Cardiovasc Interv. 2008 Aug 1;72(2):143-8.

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.

Doble B, Blackhouse G, Goeree R, Xie F. Cost-effectiveness of the Edwards SAPIEN transcatheter heart valve compared with standard management and surgical aortic valve replacement in patients with severe symptomatic aortic stenosis: a Canadian perspective. J Thorac Cardiovasc Surg. 2012 Jul 11. Epub ahead of print.

Reynolds MR, Magnuson EA, Lei Y, Wang K, Vilain K, Li H, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) Trial (Cohort A). J Am Coll Cardiol. 2012;60(25):2683-92.

Incorrect/no comparator

Gurvitch R, Wood DA, Tay EL, Leipsic J, Ye J, Lichtenstein SV, et al. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. Circulation [Internet]. 2010 Sep 28 [cited 2012 Dec 4];122(13):1319-27. Available from: http://circ.ahajournals.org/content/122/13/1319.full.pdf+html

Ye J, Cheung A, Lichtenstein SV, Nietlispach F, Albugami S, Masson JB, et al. Transapical transcatheter aortic valve implantation: follow-up to 3 years. J Thorac Cardiovasc Surg. 2010 May;139(5):1107-13.

Alli OO, Booker JD, Lennon RJ, Greason KL, Rihal CS, Holmes DR, Jr. Transcatheter aortic valve implantation: assessing the learning curve. JACC Cardiovasc Interv. 2012 Jan;5(1):72-9.

Bauer F, Lemercier M, Zajarias A, Tron C, Eltchaninoff H, Cribier A. Immediate and long-term echocardiographic findings after transcatheter aortic valve implantation for the treatment of aortic stenosis: the Cribier-Edwards/Edwards-Sapien valve experience. J Am Soc Echocardiogr. 2010;23(4):370-6.

Heuvelman HJ, van Geldorp MW, Kappetein AP, Geleijnse ML, Galema TW, Bogers AJ, et al. Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study. Neth Heart J. 2012 Aug 3;20:487-93.

APPENDIX 7: CHARACTERISTICS OF INCLUDED STUDIES

Table A1: Characteristics of Included Studies

First Author Year Country	Study Design Length of Follow-up	Intervention Versus Comparator; Number of Patients (n)	Patient Characteristics	Main Outcomes Reported in the Context of This Report
Jilaihawi et al.[21] 2012 US	Meta-analysis Up to 2 years	TAVR using the Medtronic CoreValve (n = 1,802) or the Edwards Sapien valve (n = 3,222) versus SAVR (n = 3,512)	High-risk and elderly patients with aortic stenosis TAVR mean age: 81.4 (± 7.1) years SAVR mean age: 81.9 (± 4.4) years	2-year mortality
Kodali et al.[22] 2012 US	RCT (PARTNER trial) Up to 2 years	TAVR using Edwards Sapien valve (n = 348) versus SAVR (n = 351)	High-risk patients with severe aortic stenosis Patients were considered at high surgical risk if they had coexisting conditions that were associated with a risk of death of at least 15% by 30 days after the operation. Mean age of overall study population: 84.1 (± 6.6) years	2-year mortality; repeat hospitalization; stroke or TIA; myocardial infarction; major vascular complication; major bleeding; endocarditis; renal failure; new pacemaker; SVD requiring surgical replacement
Makkar et al.[23] 2012 US	RCT (PARTNER trial) Up to 2 years	TAVR using Edwards Sapien valve (n = 179) versus standard non-surgical therapy (n = 179)	Elderly patients with severe aortic stenosis Mean age of overall study population: 83 years	2-year mortality; repeat hospitalization; stroke; NYHA class III or IV; myocardial infarction; renal failure; major bleeding; balloon aortic valvuloplasty; aortic valve replacement; endocarditis; new pacemaker

Table A1: Characteristics of Included Studies				
First Author Year Country	**Study Design Length of Follow-up**	**Intervention Versus Comparator; Number of Patients (n)**	**Patient Characteristics**	**Main Outcomes Reported in the Context of This Report**
Miller et al.[24] 2012 US	RCT (PARTNER trial) Up to 3 years	TAVR using Edwards Sapien valve (n = 344) versus SAVR (n = 313)	Subgroup of PARTNER trial; patients experiencing neurologic events	TIA; major CVA; minor CVA
Wenaweser et al.[25] 2011 Switzerland	Non-randomized study Up to 30 months	TAVR using Edwards Sapien valve or Medtronic CoreValve (n = 257) versus medical treatment (n = 78) versus SAVR (n = 107)	Elderly patients with severe aortic stenosis TAVR mean age: 82.1 (± 6.2) years Medical treatment mean age: 83.2 (±5.7)years SAVR mean age: 79.7 (±5.5) years	30-month mortality; cardiovascular death; major stroke; myocardial infarction

CVA = cerebrovascular accident; IV = intravenous; n = number; NYHA = New York Heart Association; RCT = randomized controlled trial; SAVR = surgical aortic valve replacement; SVD = structural valve deterioration; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

APPENDIX 8: SUMMARY OF CRITICAL APPRAISAL OF INCLUDED STUDIES

Table A2: Summary of Critical Appraisal of Included Studies

First Author Publication Year	Strengths	Limitations
Systematic Review		
Jilaihawi et al.[21] 2012	• a meta-analysis was done • a priori design was provided • comprehensive literature search • status of publication was used as an inclusion criterion • independent data extractors • list of included studies provided • characteristics of included studies provided • methods to combine findings were appropriate • conflict of interest was stated	• studies of different designs were pooled together • quality of the included studies not documented • list of excluded studies not provided • unsure if likelihood of publication bias was assessed
Trials		
Kodali et al.[22] 2012 (PARTNER trial)	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described • patients randomized • study had sufficient power to detect a clinically important effect	• study patients were not blinded to the intervention that they received • unclear whether the randomized intervention assignment was concealed from both patients and health care staff • characteristics of patients lost to follow-up were not described • unable to determine if randomization assignment was concealed
Makkar et al.[23] 2012 (PARTNER trial)	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described	• standard therapy not described • study patients were not blinded to the intervention that they received • unclear whether the randomized intervention assignment was concealed from both patients and health care staff • characteristics of patients lost to follow-up were not described

Table A2: Summary of Critical Appraisal of Included Studies		
First Author Publication Year	**Strengths**	**Limitations**
	• estimates of random variability and actual probability values provided • losses to follow-up described • patients randomized • study had sufficient power to detect a clinically important effect	• unable to determine if randomization assignment was concealed
Miller et al.[24] 2012 (PARTNER trial)	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described • patients randomized • study had sufficient power to detect a clinically important effect	• study patients were not blinded to the intervention that they received • unclear whether the randomized intervention assignment was concealed from both patients and health care staff • characteristics of patients lost to follow-up were not described
Wenaweser et al.[25] 2011	• hypothesis clearly described • method of selection from source population and representation described • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • losses to follow-up described	• patients not randomized • unclear whether power calculation was performed to determine adequate sample size

APPENDIX 9: MAIN STUDY FINDINGS AND AUTHORS' CONCLUSIONS

Table A3: Main Study Findings and Authors' Conclusions		
First Author Publication Year	**Main Study Findings**	**Authors' Conclusions**
Comparative Long-Term (> 12 months) Durability and Clinical Effectiveness		
Meta-Analysis		
Jilaihawi et al.[21] 2012	**Mortality from any cause at 2 year follow-up**: number of patients (percentage) SAVR: 189 (23.30) TAVR: 39 (26.50) *P* = 0.54	**"***No difference was observed in SAVR and TAVR outcomes overall for 2 year mortality*." (p. 132)
Trials		
Kodali et al.[22] 2012	**At 2-years follow-up** **Mortality from any cause:** number of patients (percentage) SAVR: 114 (35.0) TAVR: 116 (33.9) *P* = 0.78 **Mortality from cardiovascular causes:** number of patients (percentage) SAVR: 59 (20.5) TAVR: 67 (21.4) *P* = 0.80 **Repeat hospitalization:** number of patients (percentage) SAVR: 60 (21.7) TAVR: 74 (24.7) *P* = 0.41 **Stroke or TIA:** number of patients (percentage) SAVR: 18 (6.5) TAVR: 34 (11.2) *P* = 0.05 **Myocardial infarction:** number of patients (percentage) SAVR: 4 (1.5) TAVR: 0 *P* = 0.05 **Major vascular complication** number of patients (percentage) SAVR: 13 (3.8) TAVR: 40 (11.6) *P* < 0.001 **Major bleeding:** number of patients (percentage) SAVR: 95 (29.5) TAVR: 60 (19.0) *P* = 0.002	*"A 2-year follow-up of patients in the PARTNER trial supports TAVR as an alternative to surgery in high-risk patients. The two treatments were similar with respect to mortality, reduction in symptoms, and improved valve hemodynamics, but paravalvular regurgitation was more frequent after TAVR and was associated with increased late mortality."* (p. 1,686)

Table A3: Main Study Findings and Authors' Conclusions		
First Author Publication Year	**Main Study Findings**	**Authors' Conclusions**
	Endocarditis: number of patients (percentage) SAVR: 3 (1.0) TAVR: 4 (1.5) *P* = 0.61 **Renal failure :** number of patients (percentage) SAVR: 21 (6.9) TAVR: 20 (6.2) 0.75 **New pacemaker:** number of patients (percentage) SAVR: 19 (6.4) TAVR: 23 (7.2) *P* = 0.69 **SVD requiring surgical replacement:** number of patients (percentage) SAVR: 0 TAVR: 0 **Echocardiographic findings:** *Valves hemodynamics (valve areas or mean gradients)*: similar improvements between SAVR and TAVR *Moderate or severe paravalvular aortic regurgitation* (percentage) SAVR: 0.9% TAVR: 6.9% *P* < 0.001 *Relation of aortic regurgitation to all-cause mortality in the TAVR as-treated population* (HR) HR 2.11 (95% CI, 1.43 to 3.10) *P* < 0.001	
Makkar et al.[23] 2012	**At 2 years follow-up** **Mortality from any cause:** number of patients (percentage) Standard therapy: 117 (68.0) TAVR: 77 (43.3) *P* <0.001 **Mortality from cardiovascular causes:** number of patients (percentage) Standard therapy: 100 (62.4) TAVR: 50 (31.0) *P* <0.001 **Rehospitalization:** number of patients (percentage) Standard therapy: 95 (72.5) TAVR: 53 (35.0) *P* <0.001	"*Among appropriately selected patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR reduced the rates of death and hospitalization, with a decrease in symptoms and an improvement in valve hemodynamics that were sustained at 2 years of follow-up*." (p. 1,696)

Table A3: Main Study Findings and Authors' Conclusions		
First Author Publication Year	**Main Study Findings**	**Authors' Conclusions**
	Stroke: number of patients (percentage) Standard therapy: 8 (5.5) TAVR: 22 (13.8) *P* = 0.01 **Death or stroke:** number of patients (percentage) Standard therapy: 117 (68.0) TAVR: 82 (46.1) *P* <0.001 **NYHA class III or IV:** number of patients (percentage) Standard therapy: 23/40 (57.5) TAVR: 16/95 (16.8) *P* <0.001 **Myocardial infarction:** number of patients (percentage) Standard therapy: 2 (2.5) TAVR: 2 (1.6) *P* = 0.69 **Renal failure:** number of patients (percentage) Standard therapy: 9 (7.6) TAVR: 5 (3.2) *P* = 0.15 **Major bleeding:** number of patients (percentage) **Standard therapy**: 25 (20.1) TAVR: 48 (28.9) *P* = 0.09 **Balloon aortic valvuloplasty:** number of patients (percentage) Standard therapy: 140 (85.3) TAVR: 4 (2.8) *P* <0.001 **Aortic valve replacement:** number of patients (percentage) Standard therapy: 11 (8.9) TAVR: 1 (0.9) *P* = 0.005 **Endocarditis:** number of patients (percentage) Standard therapy: 1 (0.8) TAVR: 3 (2.3) *P* = 0.32 **New pacemaker:** number of patients (percentage) Standard therapy: 14 (8.6) TAVR: 10 (6.4) *P* = 0.47	

Table A3: Main Study Findings and Authors' Conclusions		
First Author Publication Year	**Main Study Findings**	**Authors' Conclusions**
	Echocardiographic findings *Valves hemodynamics (valve areas or mean gradients)*: similar improvements between standard therapy and TAVR *Moderate or severe paravalvular aortic regurgitation* (percentage) TAVR: 4.5%; similar values for standard therapy group (no values reported) *Moderate or severe transvalvular aortic regurgitation* (percentage) TAVR: 4.5%; similar values for standard therapy group (no values reported)	
Miller et al.[24] 2012	**At 3 years follow-up** **Neurologic events:** number of events **SAVR** TIA: 4 Minor CVA: 1 Major CVA: 11 Total: 16 **TAVR** TIA: 8 Minor CVA: 5 Major CVA: 18 Total: 31	*"Neurologic complications occurred more frequently after TAVR than AVR early, but thereafter the risk was influenced by patient- and disease-related factors."* (p. 832)
Wenaweser et al.[25] 2011	**At 30 months follow-up** TAVR versus medical therapy (adjusted HR) All-cause death: 0.38 (95% CI, 0.25 to 0.58) $P < 0.001$ Cardiovascular death: 0.25 (95% CI, 0.15 to 0.40) $P < 0.001$ All-cause death or major stroke: 0.39 (95% CI, 0.26 to 0.60) $P < 0.001$ All-cause death, major stroke, or MI: 0.39 (95% CI, 0.26 to 0.60) $P < 0.001$	*"Among patients with severe AS with increased surgical risk, SAVR and TAVI improve survival and symptoms compared with MT. Clinical outcomes of TAVI and SAVR seem similar among carefully selected patients with severe symptomatic AS at increased risk."* (p. 2,151)

AS = aortic stenosis; CVA = cerebrovascular accident; HR = hazard ratio; MI = myocardial infarction; MT = medical treatment; SAVR = surgical aortic valve replacement; SVD = structural valve deterioration; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

APPENDIX 10: SUMMARY AND LIST OF RELEVANT CONFERENCE ABSTRACTS

Methods

A limited literature search for abstracts was conducted using Embase. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and November 27, 2012.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the findings.

Results

The higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs and non-randomized studies.

Two RCTs and eight non-randomized studies regarding the long-term (> 12 months) outcomes of TAVR in patients with severe aortic stenosis were identified. No health technology assessments, systematic reviews, or meta-analyses were identified.

Overall Summary of Findings

Clinical Effectiveness

The two identified RCTs[29,30] represented two different cohorts of the PARTNER trial. Kodali et al.[25] reported on gender-specific differences in patients undergoing either TAVR or standard therapy. They found that there were no gender-specific differences in outcomes at two years. Patients undergoing TAVR had a lower rate of mortality and repeat hospitalization at two years (statistical significance not reported). Williams et al.[30] reported on gender-specific differences in patients undergoing either TAVR or SAVR. Women undergoing TAVR had statistically significant better two-year survival outcomes than women treated with SAVR. Men undergoing TAVR had similar mortality to men treated with SAVR. There were no significant treatment-gender differences for stroke at two years.

Three non-randomized studies reported on the long-term clinical effectiveness of TAVR compared with medical therapy,[31] TAVR compared with SAVR,[32] and TAVR compared with either medical treatment or SAVR.[33] The first study[31] found that all-cause mortality at two years was significantly less for patients treated with TAVR compared with those receiving only medical therapy. The second study[32] found that there was no significant difference in three-year overall mortality or cardiac mortality between TAVR and SAVR groups. The third study[33] reported that two-year functional outcomes (NYHA scores) for those treated with TAVR were similar to those treated with SAVR, and were significantly better (P = 0.032) than those receiving only medical treatment.

Overall, patients receiving TAVR demonstrated similar two and three-year outcomes to those receiving SAVR, and had significantly better mortality outcomes than those patients receiving only standard medical treatment.

Long-Term Durability

Five non-randomized studies[34-38] reported on long-term durability of valves used in the TAVR procedure. One study[34] found that the Medtronic CoreValve remained stable, with no structural valve deterioration observed at three years of follow-up. One study[35] reported on both the Medtronic CoreValve and the Edwards Sapien valve, and found no structural valve deterioration in up to five years of follow-up. A third study[36] found that the Sapien/Sapien XT valve remained durable at four years of follow-up. A study from the United Kingdom[37] reported that there was no significant function deterioration in valves at four years of follow-up, but the study did not specify which valves were used in the TAVR procedures. The fifth study[38] examined four-year durability of the 21-Fr TAVI valve, and reported that there was no structural deterioration or frame fractures after four years of follow-up.

Overall, the valves used in TAVR procedures were found to have successful long-term durability at three, four, and five years.

List of References Summarized

RCTs

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Non-Randomized Studies

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