

Transcatheter Aortic Valve Implantation (TAVI)
for the Treatment of Aortic Valve Stenosis:
a Systematic Review

by

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Abstract

Introduction: Aortic stenosis (AS) is the most common form of heart valve disease in the western world. As the population ages, this disease is becoming an increasing burden on patients and on the health care system. Current drug therapies (medical management (MM)) cannot reverse the course of AS. For most individuals with severe AS, surgical aortic valve replacement (SAVR), which requires open heart surgery and cardiopulmonary bypass, remains the standard therapy. However, a sub-group of patients with aortic stenosis are unsuitable for or at high risk to undergo SAVR due to their frailty or other comorbidities. Transcatheter aortic valve implantation (TAVI) - a novel, less invasive treatment option – was developed as an alternative for patients who are not suitable or at high risk for undergoing surgery.

Objective: This study is intended to assess the feasibility, safety, efficacy and clinical effectiveness of TAVI, using the transfemoral (TF) and transapical (TA) approaches, in comparison to medical management or SAVR in patients with severe symptomatic AS; and to compare the outcomes associated with the two different approaches for valve implantation (TF and TA).

Methods: A comprehensive literature search was conducted using eight electronic databases to identify studies of TAVI (TF and/or TA) for the treatment of AS. Data from the selected studies were extracted by two reviewers. Outcomes considered were feasibility, safety, efficacy and effectiveness of TAVI. Study quality was assessed and information was tabulated to identify trends or patterns. Results were pooled across studies for each outcome.

Results: Fifty six relevant studies were identified: 37 studies (including seven comparative studies) assessed clinical outcomes, 14 studies discussed health-related quality of life, and five studies examined the impact of the learning curve on feasibility and safety of TAVI on patient outcomes.

The overall procedural success rate was 96% (88% - 100%). Studies that examined the learning curve for TAVI demonstrated it had a significant impact - increasing the procedural success rate and decreasing 30-day mortality. The mean combined periprocedural and cumulative all-cause mortality rate at 30 days for TAVI compared to the control groups (MM and/or SAVR) in the same or different studies was 9.0%, n = 10,500 vs 2.8%, n = 179, and 6.7%, n = 302, respectively. Permanent pacemaker implantation was three times more common with the Medtronic CoreValve compared to the Edwards SAPIEN prosthesis (26.5% vs 8.2%), but when both TAVI valves were compared with SAVR, there was no statistically significant difference. Major vascular complications occurred more frequently in the TF group (11.6%) than in the MM, SAVR or the TA groups. The rate of acute kidney injury requiring renal replacement therapy did not differ significantly between the TAVI and control groups, but was three times higher with the TA compared to the TF approach (7.3% vs 2.5%). TAVI achieved significant hemodynamic improvement as measured by echocardiography. The pooled estimate for moderate or severe paravalvular aortic regurgitation after TAVI was 7.2% (with no significant difference between TAVI approaches). Paravalvular aortic regurgitation occurred more frequently with TAVI than with SAVR.

One year survival rates ranged from 68% to 77% for TAVI patients in the comparative studies and 72% to 85.3% in the case series studies. For MM and SAVR, the one year

survival rate was 45% to 49.7% and 73.4% to 83%, respectively. Studies that compared patients' quality of life before and after TAVI found significant improvement at one-year follow-up.

Conclusions: TAVI offers a safe and effective treatment for severe aortic stenosis in patients who are not suitable for or are at high risk to undergo SAVR. Unfortunately, current shortcomings in the evidence on long term outcomes make it difficult to determine the effectiveness of TAVI in high risk patients who may be candidates for surgery.

Preface

This thesis is an original work by Pedro Pimentel Sad. The research project received ethics approval from the University of Alberta Research Ethics Board, Project Name “Health Technology Assessment Dissertation on Transcatheter Aortic Valve Implantation”, No. Pro00029730, July 11, 2012. No part of this thesis has been previously published.

Dedication

This thesis is dedicated to my wife, Fatima Coeli Soares Sad, and to my daughter, Isis Rowena. Their support, patience and understanding have motivated me to finish this thesis.

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Abbreviations

AHCIP = Alberta Health Care Insurance Plan

AKI = acute kidney injury

AS = aortic stenosis

ATIH = Agence Technique de l'Information sur l'Hospitalisation

AVA = assessment of aortic valve area

BAV = balloon valvuloplasty

CABG = coronary artery bypass graft

CCU = cardiac care unit

CK = creatine kinase

CLC = clinical cardiologist

CT = computed tomography

CVVHD = continuous venovenous hemodialysis

dL = decilitre

ECG = electrocardiogram

ELS = Edwards Lifesciences

EMS = emergency medical services

FDA = US Food and Drug Administration

FH = first half

GP = general practitioner

h = hour

HRQoL = health-related quality of life

HTN = hypertension

ICU = intensive care unit

ITT = intention to treat

KCCQ = Kansas City Cardiomyopathy Questionnaire

LBBB = left bundle branch block

LV = left ventricle

MDT = multidisciplinary team

MI = myocardial infarction

MLHF = Minnesota Living with Heart Failure Questionnaire

NIH = US National Institutes of Health

NRT = non-randomized trial

NYHA = New York Heart Association

OCCI = Ontario Case Costing Initiative

OHIP = Ontario Health Insurance Plan

PARTNER = Placement of Aortic Transcatheter Valve Trial (PARTNER A and B)

PICOS = Patients / Intervention(s) / Comparator(s) / Outcomes / Study design

PPM = permanent pacemaker implantation

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT = randomised controlled trial

RRT = renal replacement therapy

SAVR = surgical aortic valve replacement

SC = subclavian

SH = second half

TA = transapical

TAO = transaortic

TAVI = transcatheter aortic valve implantation

TF = transfemoral

TIA = transient ischemic attack

U = unit

URL = upper reference unit

VARC = Valve Academic Research Consortium

VC = vascular complications

Chapter 1. Introduction

1.1 Overview of aortic stenosis (AS)

Cardiovascular diseases account for approximately one-third of all deaths in Canada each year.^{1,2} Calcific aortic stenosis (AS) is the third most common form of cardiovascular disease in Western countries after hypertension (high blood pressure) and coronary artery disease,³ and the most common form of age-related heart valve disease¹ – consequently, it is a major cause of cardiovascular morbidity and mortality.⁴

1.1.1 Clinical background

The aortic valve is one of four valves in the heart acting as a portal for the flow of blood between the left ventricle and the aorta. When the left ventricle contracts (systole), the aortic valve opens allowing the outflow of blood to the aorta and to the body. When the aortic valve closes it prevents the backflow of blood to the heart, the left ventricle expands (diastole), and it is filled with incoming blood from the lungs through the left atrium across the mitral valve.

The gradual obstruction of the left ventricular outflow caused by a progressive narrowing of the aortic valve leads to a condition called aortic stenosis (AS). Individuals with AS remain asymptomatic during the latency period while the disease progresses insidiously, narrowing the aortic valve. This increases the left ventricular pressure required by the heart to eject blood into the circulatory system. Eventually, severe calcification thickens the three leaflets of the aortic valve, increasing resistance and impairing blood flow.⁴⁻⁹

In addition to calcific AS, the other two forms of AS are congenital bicuspid, a form of premature calcification prevalent in the younger age group,¹⁰ and rheumatic AS, a condition which is now relatively uncommon in industrialised countries (Figure 1).^{10,11}

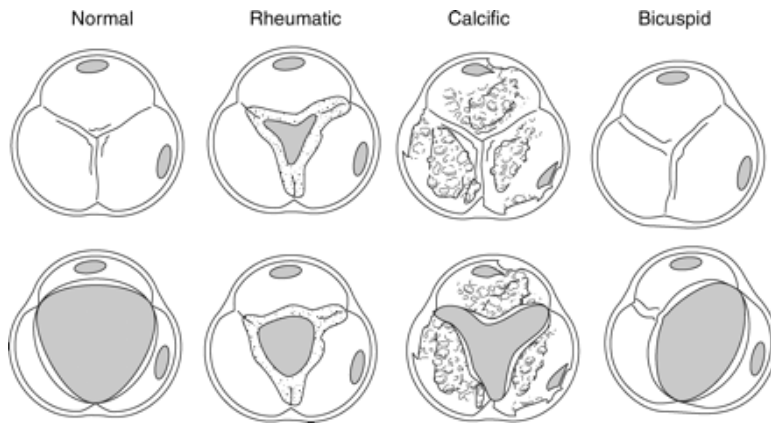


Figure 1. Aortic stenosis etiology: morphology of a normal, rheumatic, calcific and bicuspid AS

Source: Baumgartner H, et al.¹²

1.1.2 Risk factors

Calcific aortic stenosis is more common in elderly patients and studies suggest that the rate of AS progression in males is faster than in females.^{13,14} Other factors associated with the development of AS are hypertension, diabetes mellitus, elevated serum calcium, elevated creatine, total cholesterol, triglycerides and lipoproteins.^{13,15-20} Obesity and smoking are independent risk factors that increase the risk of aortic stenosis.¹⁹ Notably, hypertension, old age and coronary artery disease were among the risk factors with the highest incidence associated with AS at the baseline characteristics of all patients included in this thesis.

1.1.3 Natural course of aortic stenosis

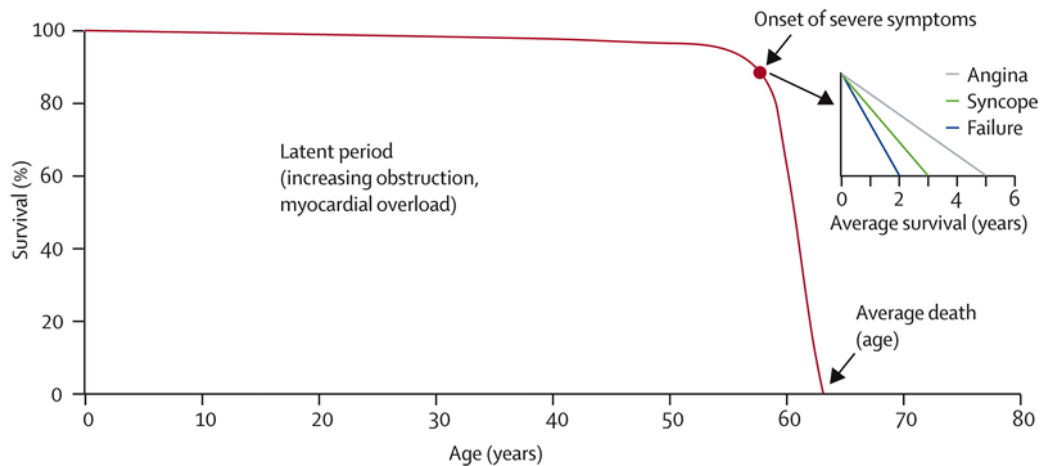
A normal aortic valve in adults consists of three cusps with an orifice from three to four cm² when open. Obstruction caused by AS has a prolonged latency period during which outcomes remain similar to those for unaffected age-matched adults.²¹ Several hemodynamic studies have estimated the progression rate of valve stenosis in individuals with moderate AS using a Doppler echocardiographic examination and cardiac catheterization.^{3,22,23} According to their findings, some patients exhibited a decrease in valve area of 0.1 to 0.3 cm² per year with the average rate of change of approximately 0.12 cm² per year.⁵ Until the valve area has decreased by 50%, stenosis may occur over a period of decades (the latency period) without affecting the flow.

While a normal aortic jet velocity is less than 2.5 m/s, in AS, the velocity of blood crossing the valve will be greater because of the increased pressure gradient to compensate for the narrowing of the valve.²⁴ Once the pressure gradient of the aortic jet is greater than 4.0 m/sec and the valve area is less than 1.0 cm², the outlook changes significantly and the classic symptoms of angina, syncope and congestive heart failure are likely to occur.^{10,25-27}

Once symptoms occur the prognosis is poor marking a critical point in the natural history of AS. Survival curves below show that the interval from the onset of symptoms to the time of death is approximately five years in patients with angina, three years in those with syncope and two years in those with congestive heart failure (Figure 2).²⁸ Overall, if left untreated, severe symptomatic aortic stenosis, may reach a 75% mortality rate within 3 years of symptom onset.²⁹ In an RCT that enrolled patients who were considered unsuitable for surgical aortic valve replacement (SAVR), the one-year and two-year all-cause mortality rate was 50% and 68%, respectively.^{30,31}

Figure 2. Natural course of aortic valve stenosis without treatment

Source: Ross J et al.²⁸



Aortic stenosis is mainly detected during clinical examination; the high pressure blood flow through the valve can be characterized by a murmur during the period of left ventricular contraction (systole).²³ This sound is the most typical sign of aortic stenosis, usually loudest at the upper sternal border that peaks late and radiates to the right

carotid artery.³² Based on this finding, diagnosis is confirmed with Doppler echocardiography which assesses the severity of the stenosis by measuring the aortic valve area, peak and mean transvalvular gradients and maximum aortic jet velocity.²⁴

The American College of Cardiology and the American Heart Association guidelines define the degree of aortic stenosis as mild, moderate or severe based upon the valve area, the mean pressure gradient across the valve and on aortic jet velocity (see Table 1).²⁴

Table 1. Grading the severity of aortic stenosis in adults			
Severity	Valve area (cm ²)	Pressure gradient (mm Hg)	Jet velocity (m per second)
Mild	>1.5	< 25	< 3.0
Moderate	1.0 - 1.5	25 - 40	3.0 - 4.0
Severe	<1.0	> 40	> 4.0

1.2 The burden of disease

1.2.1 Prevalence

After hypertension and coronary disease, calcific AS is the most common cardiovascular disease in Western countries,³³ with an increasing prevalence as the population ages.^{34,35} A recent meta-analysis and systematic review reports that the prevalence of severe AS is 3.4% of adults over the age of 75.³⁵ As the total Canadian population aged 75 and higher is 2,351,025 (according to Canadian census 2012),³⁶ severe AS may be present in 79,935 people; and among these patients with severe AS an estimated 75.6%³⁵ (60,430) would have severe symptomatic AS. The current population of Albertans aged 75 and higher is 193,995.³⁷ Consequently, an estimated 3.4% or 6,595 Albertans may have severe AS and 75.6%³⁵ of these individuals (4,986) would be symptomatic.

1.2.2 Incidence

Although studies have analysed the prevalence and progression of AS, information on its incidence is scarce.³⁸ One study found an incidence of AS of 4.9% per year, but the authors acknowledged that the “voluntary-based screening method” they

used may have biased these results; as this type of method only included people who voluntarily attended screening some people may have chosen not to participate.³⁸

1.2.3 Health-related quality of life (HRQoL)

Preoperative patients with symptomatic AS report diminished HRQoL in both physical and mental domains, regardless of age, compromising their normal daily activities.³⁹ One study compared a group of symptomatic patients with a group of asymptomatic patients, both with severe AS.³⁹ The two groups completed a standardized questionnaire used to measure health status in mental, physical, social and general health domains. While asymptomatic patients had health scores comparable to those of the general population, the symptomatic group scored considerably lower across the different domains.³⁹

1.2.4 Health care costs

As the latency period of AS is asymptomatic it is unlikely that there would be an increase in hospitalisation, resulting in little incremental direct or indirect costs during this period. However, with the onset of the classic symptoms of syncope, angina and congestive heart failure emerge, AS incurs substantial health care costs.

A recent study reported that an estimated 40.5% of patients with severe symptomatic AS may not undergo surgery, thus becoming potential candidates for medical management.³⁵ As the Canadian elderly population with severe symptomatic AS is 60,430 (see section 1.2.1 above), 40.5% (24,474) of these patients would likely become candidates for medical management. Likewise, in Alberta an estimated 75.6% (4,986) would have severe symptomatic AS, and of these, 2,019 (40.5%) would not undergo surgery, thus becoming candidates for non-surgical options.

A 2013 Canadian study examined the effect of symptomatic AS on health expenditures⁴⁰ specifically the cost-effectiveness of TAVI compared to medical management in inoperable patients with severe AS. The study found the total cost associated with the management of a single patient with severe symptomatic AS over a three-year period was \$58,537, or \$19,452 CAD per year.⁴⁰ These findings suggest that the aggregate

annual cost associated with the medical management of patients with AS for 2013 was approximately \$476 million CAD in Canada and \$39 million CAD in Alberta.

1.3 Treatment options and their limitations

1.3.1 Surgical aortic valve replacement (SAVR)

Once patients develop severe symptoms of aortic stenosis (i.e. angina and shortness of breath) SAVR is considered the standard of care.²⁴ During the surgery the stenotic valve is removed and replaced with a biological or mechanical valve. This is a major surgical procedure which requires an incision along the sternum (sternotomy) and the need for cardiopulmonary bypass.⁴¹ Despite its effectiveness, SAVR is associated with a significant risk of morbidity and mortality, particularly in patients with comorbidities.^{42,43} Some of the conditions that increase the surgical risk include previous cardiac surgery, chronic obstructive airway diseases, peripheral vascular disease, poor left ventricular function, previous stroke, renal failure, diabetes and hypertension.⁴⁴ Another important factor for consideration is frailty; although no current consensual definition of frailty exists,^{45,46} most authors agree that frailty makes a patient particularly vulnerable to undergo surgery.⁴⁷

Surgical aortic valve replacement remains the gold standard for the treatment of severe aortic stenosis with approximately 100,000 aortic valve operations performed annually in North America.⁴⁸ By comparison, in 2006/2007, 335 aortic valve replacements were performed in the province of Alberta.⁴⁹ A successful SAVR procedure results in a life expectancy similar to that of the general population,⁵⁰ with a current mortality risk ranging from 2 to 5%.^{33,51} However, given the risk factors associated with surgery, a high proportion of patients (33 to 41%) are not considered eligible for SAVR.^{52,53}

1.3.2 Medical management (MM)

Patients with severe symptomatic AS who are not suitable for surgery are potential candidates for medical management.¹⁰ Studies have indicated that the aortic valve becomes stenotic due to an active inflammatory process similar to that of atherosclerosis.^{29,54-56} Therapies for delaying progression of coronary artery disease, particularly statins, have been investigated for similar effects in patients with calcific AS.⁵⁴

As a type of cholesterol reducing drug, statins inhibit a key liver enzyme involved in making cholesterol.⁵⁷ The retrospective observational studies found that patients receiving statins had lower rates of disease progression as measured by changes in peak gradient, mean gradient and aortic valve area compared to patients who did not receive statins.^{17,55,58} These observational studies provided justification for randomised trials to substantiate whether statin therapy could effectively reduce or stop the progression of AS.^{59,60} Two trials subsequently provided evidence that statins did not reduce the progression of AS in patients with mild to moderate calcific AS.^{59,60} These findings were confirmed by a third randomised trial conducted in Canada.⁶¹ Currently, no medical therapy effectively alters the progression of the disease or contributes to additional survival for patients with mild to moderate or severe calcific AS.^{4,62}

1.3.3 Balloon valvuloplasty (BAV)

Introduced in 1985, BAV is a non-surgical procedure used as an alternative approach in patients not deemed suitable for surgical aortic valve replacement.⁶³ This technique has demonstrated short term relief of symptoms and temporary improvement of valvular function in inoperable patients without altering the natural course of the disease.^{30,64,65}

BAV widens the stenotic valve using an inflation balloon to reduce the degree of stenosis. This technique consists of attaching a deflated balloon to a catheter, then passing it through the aorta until it reaches the stenotic valve.⁴⁹ After x-rays assure the catheter and balloon are placed at the right location, the inflating balloon stretches and cracks the stenotic valve in an attempt to reduce the degree of stenosis, allowing the blood to flow out more easily. Once the procedure is completed, the balloon is deflated and removed.^{63,66}

Complications associated with BAV, such as stroke, heart attack, the risk of restenosis and the absence of long-term survival benefits, reduce its value as an effective procedure.^{66,67} In a recent trial of BAV, where 82.3% of medically managed patients unsuitable for surgery received this intervention, the one-year mortality rate in the BAV group was close to 50%.³⁰ The American College/American Heart Association guidelines

recommend that BAV be used either as a treatment option for palliative care, a bridge to SAVR,^{22,68} or more recently as a bridge to TAVI.⁶⁹⁻⁷¹

1.3.4 Transcatheter aortic valve implantation (TAVI)

TAVI was first performed in 2002, using the transeptal route, a technically demanding procedure that requires access through the femoral vein.⁴² Since then, other delivery systems have been developed. TAVI represents a less invasive alternative to SAVR for the treatment of severe symptomatic AS in patients at high risk or not suitable for SAVR.⁷² With careful patient selection, this technique has been performed in more than 40 countries on over 50,000 patients.⁷³ Where possible, TAVI is used in preference to medical management or BAV.⁷⁴

The Canadian Cardiovascular Society recommends that patients who are possible candidates for TAVI be assessed by a multidisciplinary team that includes expertise in interventional cardiology, cardiac surgery, diagnostic imaging, cardiac anesthesiology and cardiac nursing.⁷⁵

1.3.4.1 Approaches used for TAVI

Transfemoral (TF) procedure

The first transfemoral artery TAVI procedure was performed in 2005.⁷⁶ Associated with less surgical trauma, this route is a more feasible procedure, similar to that used for other minimally invasive cardiac interventions.^{77,78}

An accurate evaluation of the iliofemoral anatomy is crucial for the success of this approach.⁷² First the stenotic valve is dilated using a balloon catheter, which is advanced through a percutaneous route. At this time, a bioprosthesis, crimped onto a delivery catheter for implantation of the valve is inserted through a sheath placed in the femoral artery through the common iliac artery and aorta until it reaches the stenotic valve retrogradely.⁷⁹ This procedure is performed in either a cardiac catheterization laboratory or in a hybrid operating room (an operating room with advanced imaging equipment that allows minimally invasive surgical procedures as well as traditional surgery).⁸⁰ Most centres that perform TAVI favour TF as the preferred route because it is the least invasive approach (Figure 3a).⁷²

Transapical (TA) procedure

In 2006, the first transapical aortic implantation (TA) was introduced as an alternative to the TF route when cardiovascular complications (e.g., atherosclerosis, porcelain aorta, coronary artery disease) make the TF route extremely challenging.^{81,82 83,84}

The TA approach requires a small left lateral incision, usually between the fifth and sixth intercostal space, to expose the apex of the heart followed by a direct puncture of the left ventricular apex. The delivery catheter is placed and advanced through the left ventricular apex crossing the stenotic valve antegradely (Figure 3b).⁷²

Transaortic (TAO) procedure

In 2009 and 2010, this route was suggested as an alternative to the transapical approach for patients with no peripheral artery access.⁸⁵⁻⁸⁷ TAO is performed through a small right or mid-sternotomy between the ribs. Then, a valve delivery catheter is advanced towards the heart through the ascending aorta retrogradely (Figure 3c).⁷²

Subclavian (SC) procedure

The subclavian approach was developed as an alternative to the transfemoral approach with the CoreValve® system.^{88,89} A surgical cut-down is needed to isolate the subclavian artery. The valve is then implanted using a delivery catheter which advances the valve through the left subclavian artery towards the stenotic valve for positioning and deployment (Figure 3d).⁷²

Transaxillary procedure

Although it does not have widespread clinical acceptance, the transaxillary approach is another alternative to the transfemoral approach.⁹⁰ Like the subclavian approach, it requires a surgical cut-down to isolate the left axillary artery. The sheath and delivery catheter advances the valve through the left axillary artery retrogradely (Figure 3e).⁷²

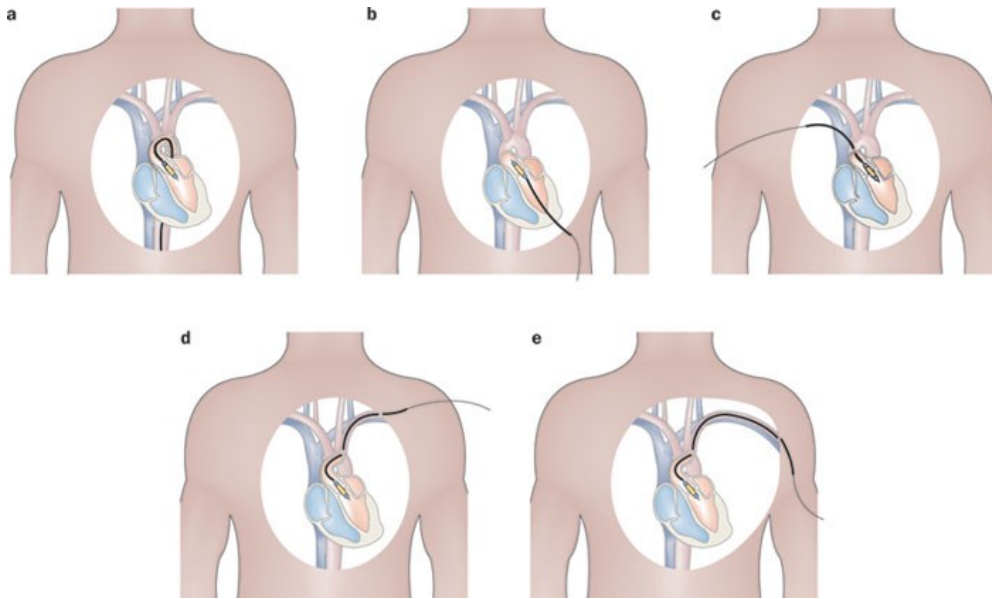


Figure 3. Different approaches used for TAVI

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Currently, the two most widely used approaches are transfemoral and transapical.⁷²

1.3.5 Valve types

Several different transcatheter aortic valves have been developed or are in various stages of commercial development worldwide.^{72,91} In North America to date, two manufacturers have received regulatory approval to market transcatheter aortic valves.

These are the TAVI valves most commonly used in clinical practice:

- The balloon expandable Edwards SAPIEN and Edwards SAPIEN XT® (Edwards Lifesciences, Irvine, CA, US).
- The self-expanding CoreValve® System (Medtronic, Minneapolis, MN, US).⁷²

Both valves have Health Canada approval for use in Canada.⁹²

Balloon-expandable Edwards valve

The three generations of the Edwards SAPIEN system comprise a tri-leaflet bovine pericardial valve.⁷² While the first two generations of the device, Cribier-Edwards and Edwards SAPIEN®, were mounted in a stainless steel balloon-expandable frame, the third generation, SAPIEN XT®, is mounted in a cobalt chromium frame.⁷² SAPIEN XT® also

contains a frame design with fewer rows and columns allowing a reduction in the valve sizes from 22 French and 24 French (7.3 mm and 8.0 mm respectively), to 18 French and 19 French delivery catheter (6.0 mm and 6.3 mm respectively) with no loss of radial strength.^{72,93,94}

Self-expanding CoreValve® System

The three generations of the CoreValve® System consist of a self-expanding leaflet nitinol stent frame in which a tri-leaflet tissue valve is mounted and sutured. The first generation used bovine pericardial tissue and was constrained within a 25 French (8.4 mm) delivery catheter.^{72,93} The second-generation used porcine tissue and a 21 French (7.0 mm) delivery catheter.^{72,93} The third-generation, also made of porcine heart tissue, has been further restructured to provide a better anatomical fit and can be implanted using an 18 French (6.0 mm) delivery catheter.^{72,93} In the US, Medtronic has Food and Drug Administration (FDA) approval for the CoreValve System. The approved indications were recently expanded to include a broader patient group from only patients who are not eligible for surgery to patients who would be at high surgical risk.^{95,96}

Objectives

This study is intended to determine the feasibility, safety, efficacy and effectiveness of TAVI in comparison to SAVR or medical management in high risk patients with severe aortic stenosis.

Research questions

The main question to be addressed in this review is:

- What is the implication of TAVI in the management of severe symptomatic aortic stenosis (AS) in adults who are unsuitable for or at high risk for SAVR?

Specific questions to be addressed are:

- What is the evidence on the safety, efficacy and effectiveness of TAVI (using either transfemoral (TF) or transapical (TA) approaches) for patients with severe symptomatic AS?
- What are the risks of complications associated with TAVI according to the two approaches (TF/TA) of valve implantation?

Chapter 2. Methods

2.1 Literature search

A comprehensive literature search for published and unpublished studies on TAVI was conducted following Cochrane Collaboration guidelines for systematic reviews.⁹⁷ The search included the following bibliographic databases: PubMed, MEDLINE, The Cochrane Library, EMBASE, Web of Science, Scopus, and the Centre for Reviews and Dissemination (DARE, Health Technology Assessment, and NHS Economic Evaluation). The search strategy combined Medical Subject Headings (MeSH) and other controlled vocabulary terms, such as “Aortic Valve Stenosis/Surgery” or “Aortic Valve/Surgery” or “Heart Valve Prosthesis” with additional free text keywords (such as the names of particular valves and surgical approaches). The search was limited to English and French language studies published from January 2002 (the year TAVI was first used in human studies) to 2012. To find grey or unpublished literature, relevant websites (such as ClinicalTrials.gov, the National Guideline Clearinghouse, the US Food and Drug Administration, and Health Canada) were searched for ongoing clinical trials, clinical practice guidelines, information on different valves and new approaches to TAVI and unpublished studies. Manufacturers’ web sites were also searched for further information (see Appendix A. Literature search strategy).

The database searches were supplemented by scanning the reference lists of key papers to identify additional studies. Contact with clinical experts in this field was sought throughout the project. Monthly update searches were run in PubMed throughout the project until August 2013.

2.2 Study selection and presentation of results

Results from the literature search were imported into the Reference Manager® (v. 12) database to remove duplicate references and manage bibliographic citations. Two reviewers independently screened the titles and abstracts of the search results to exclude irrelevant studies and identify citations which potentially met the inclusion criteria (see Table 2). Non-English and non-French language studies were excluded, as were editorials, abstracts, expert opinions and conference presentations. Unless they provided additional information on updated TAVI approaches, non-systematic reviews were not included. Following a discussion with the members of the thesis committee,

studies that included fewer than 10 patients or reported data on TAVI without specifying the type of approach used (TF or TA) were also excluded. Since the TF and TA approaches are the only approaches used in Alberta, other approaches were not considered for this analysis. Only primary studies that met the criteria listed in Table 2 were considered eligible for inclusion.

The full papers of potentially relevant studies were retrieved for review and assessed by means of an inclusion/exclusion checklist form with predetermined eligibility criteria. Study selection has been presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Appendix B, Figure 12.)⁹⁸

Parameter	Inclusion criteria	Exclusion criteria
<i>Participants</i>	<ul style="list-style-type: none"> Adults with severe AS unsuitable or at high risk for SAVR 	<ul style="list-style-type: none"> Patients with moderate risk for SAVR Asymptomatic patients
<i>Interventions</i>	<ul style="list-style-type: none"> TAVI (either TF or TA or both, with data reported separately) with the Edwards SAPIEN™, SAPIEN XT™ or Core Valve™ devices 	<ul style="list-style-type: none"> Cribier-Edwards valve (except where the inclusion represented a minority of cases) Valves not licensed in Canada Combined data for TF and TA Approaches other than TF or TA (exception made for large studies where the majority of patients were TF or where the combination of TF with another approach, in small studies, would not result in any statistically significant difference)
<i>Comparators</i>	<ul style="list-style-type: none"> SAVR, MM or none 	
<i>Outcomes</i>	<ul style="list-style-type: none"> Feasibility Safety Efficacy Effectiveness Adverse events/complications Quality of life 	
<i>Study design</i>	<ul style="list-style-type: none"> Randomized and non-randomized studies Prospective, retrospective, or matched cohort studies Case control studies or clinical series 	<ul style="list-style-type: none"> Editorials, abstracts, grey literature, review articles, expert opinion Population < 10 patients Case reports

Abbreviations: AS, aortic stenosis; MM, medical management; SAVR, surgical aortic valve replacement; TA, transapical; TF, transfemoral

2.3 Data extraction

Data from the studies were extracted by a single reviewer using a pre-tested data extraction form, and following the approach taken on published literature, data from 20%

of the studies were extracted by a second reviewer to validate the process.⁹⁹ This form contained elements to extract the purpose, methods and outcomes of each study (Table 3). When possible, intention to treat (ITT) reported data were used. When required, the study authors were contacted by electronic mail to ensure that patients were not double counted from previous studies. Disagreements were resolved through consensus between the two reviewers. Kappa values were not calculated.

Table 3. Data abstraction form elements	
Parameter	Description of information collected
Patients	Age, gender, estimated operative risk, functional class (NYHA), baseline echocardiographic data, prior treatments, comorbidities
Intervention(s)	Details of the treatment, number of patients per intervention group
Comparator(s)	SAVR, MM or none
Outcomes	Procedural success (including procedural time, valve-in-valve, conversion to SAVR and ICU/hospital stay), mortality, complications, survival, rehospitalisation, echocardiographic data, NYHA functional class, quality of life, and physician experience
Study design	Enrollment period, country, study type, study centre, length of follow-up, valve type, funding sources, TAVI approach (TF and/or TA), number of patients, comparison group

Abbreviations: ICU, intensive care unit; MM, medical management; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TA, transapical; TF, transfemoral

2.4 Critical appraisal of the studies

Two reviewers independently assessed risk of bias for the experimental studies using the Cochrane Collaboration risk of bias tool.⁹⁷ The risk of bias criteria have six domains and are rated as high risk (HR), low risk (LR) or unclear. The quality of observational studies was also assessed by two reviewers using the Oxford Centre for Evidence-based Medicine Levels of Evidence.¹⁰⁰ Disagreements between reviewers were resolved through discussion.

2.5 Outcome measures

VARC guidelines, studies identified through the literature search, and consultation with clinical experts were used to standardize the definitions of outcome measures.

Feasibility (derived from a systematic review on TAVI) was measured as the procedural success rate, valve-in-valve and conversion to surgery.¹⁰¹ Safety, efficacy, effectiveness

and quality of life definitions were derived from two studies that reported standardized outcomes for TAVI: the Valve Academic Research Consortium (VARC) and its update version (VARC 2).^{102,103}

- Safety is measured by all-cause/cardiac mortality, the avoidance^l of valve-related or procedural complications at 30 days.
- Efficacy is measured by the extent of prosthetic heart valve dysfunction using echocardiography criteria for hemodynamic monitoring, including mean aortic valve area before and after TAVI, mean pressure gradient before and after TAVI, left ventricular ejection fraction before and after TAVI and paravalvular regurgitation after TAVI, New York Heart Association (NYHA) functional class improvement versus baseline at 30-day, one year or longer reviews.
- Effectiveness is measured by the avoidance of disease-related outcomes, including mortality at one-year or longer, combined with measures of clinical functional benefit of TAVI (e.g., rehospitalisation for valve-related outcomes) at one year or longer.

To allow more robust conclusions on the efficacy and effectiveness of TAVI, the pooling method used actual data from published studies and data from studies where censored data was not statistically significant were also included.

Cardiac death and complications are defined as directly involving cardiac integrity, (e.g., heart/multi-organ failure, sudden death, arrhythmia) while non-cardiac death does not directly involve the heart (e.g., cerebrovascular, sepsis/infection or pulmonary complications).^{104,105} In accordance with the VARC consensus document “unknown” cardiovascular deaths and vascular complications (e.g., dissection/perforation), when related to the procedure, were considered as cardiovascular in origin.¹⁰² Of note, VARC guideline system proposed standardized consensus definitions to allow meaningful homogeneous comparisons among clinical studies.¹⁰²

^l The word “avoidance” is used under the VARC criteria for endpoints definitions¹⁰²

This analysis also follows VARC 2 guidelines for procedural success, which recommend capturing intra-procedural complications or outcomes including the following:¹⁰³

- Any complications that result in immediate or consequent death \leq 72 hours post-procedure
- successful access, delivery, and deployment of the device, and successful retrieval of the delivery system
- The correct implantation of a single device in the proper anatomical location
- Intended performance of the prosthetic heart valve (aortic valve area $>$ 1.2 cm² and mean aortic valve gradient $<$ 20 mmHg or peak velocity $<$ 3 m/s)
- No moderate or severe valve regurgitation

Three ways were used to identify outcomes. Short-term was defined as 30 days and long-term as one year and beyond. Advice from clinical experts was also sought to obtain a better understanding of the risks associated with TAVI and to include the most relevant outcome measures.

2.6 Health-related quality of life (HRQoL)

This thesis follows VARC-2 guidelines for TAVI (VARC-2) which recommend a comprehensive assessment of health-related quality of life.¹⁰³ VARC-2 recommends using a combination of heart failure specific measures (e.g. Kansas City Cardiomyopathy Questionnaire (KCCQ) or The Minnesota Living with Heart Failure Questionnaire (MLHF)) and one or more generic measures (e.g., the Short Form-36, the Short Form-12, or the EuroQOL (EQ-5D)).¹⁰⁶⁻¹⁰⁸

2.7 Learning curve

According to a systematic review, the learning curve is not often formally considered in health technology assessment due to the lack of rigorous statistical methods available to measure and adjust for learning.¹⁰⁹ The review concluded that, at minimum, reports of the learning curve should include the rate of procedures, the experience of the clinicians, and a description of how data was collected.¹⁰⁹ This thesis includes characteristics and

quantitative results of studies that assessed the learning curve of the physician and team involved in the implantation of TAVI using the transfemoral or transapical routes.

2.8 Data analysis and synthesis of the results

Data collected from studies were summarized in tables to better identify trends and patterns in results across studies. Results from individual studies were pooled using weighted mean values to generate summary estimates for each of the outcomes of interest. Categorical data are expressed as frequencies and percentages, data from individual studies were pooled using Excel and comparisons between groups were made using chi-square tests (when frequencies in a single cell were higher than five) or Fisher's exact test (when frequencies were less than or equal to five). Continuous data are expressed as mean \pm SD, data from individual studies were pooled using STATA, and comparisons between the two groups were made using the 2-tailed *t* test.¹¹⁰ P-values <0.05 were considered significant.

All statistical analyses were conducted with either Microsoft Excel 2010 or STATA version 12.0 (StataCorp). A meta-analysis was not performed due to the heterogeneity of outcome measures used across the studies.

2.9 Data collection - participants and interview procedures

To develop a clinical pathway in Alberta, interviews were conducted with clinical experts. The Multidisciplinary Team (MDT) of clinical experts for this review were invited to participate in interviews conducted between August and October 2012. In total, five one-on-one in-person interviews were conducted using a semi-structured questionnaire consisting of 12 questions (Table 4). The one-on-one interview technique was chosen instead of a focus-group approach to avoid the possibility of group domination by individual participants.¹¹¹ All the interviews lasted approximately 30 minutes and were conducted at the participant's workplace. To minimize potential misreporting the interviews were audio recorded and transcribed verbatim. All answers were compared and analysed to increase the likelihood of obtaining comprehensive data. Prior to the interview, respondents were informed about the study details and given assurance about anonymity and confidentiality. Ethics approval was obtained from the Health Research Ethics Board of the University of Alberta.

The first questions were relatively straight forward (e.g. types of therapies) so as to gradually lead participants to describing the local clinical pathway for TAVI patients. At this point, the proposed clinical pathway from the UK was presented to assist participants (Figure 4). Prompts were used to clarify if the responses were not complete. The questionnaire was pilot-tested with a local cardiologist.

Figure 4. Proposed clinical pathway for assessing patients for TAVI

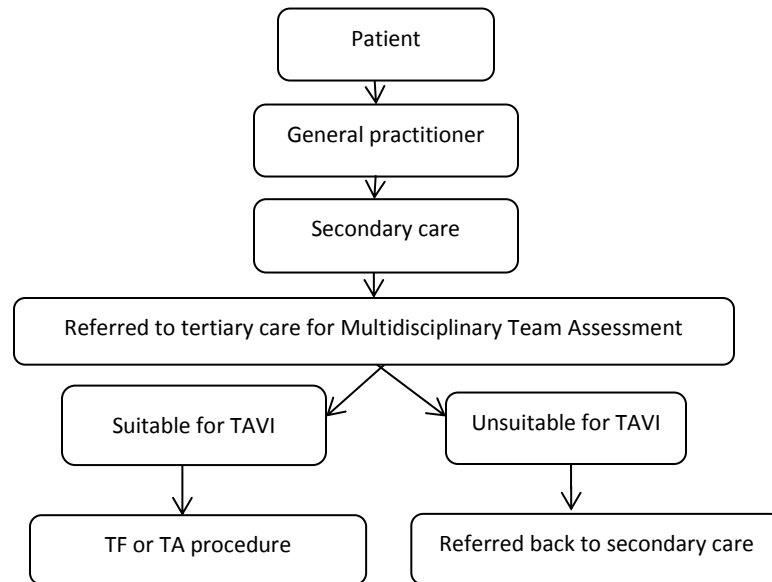


Table 4. Interview questions

1. What therapies are available for patients with severe aortic stenosis?
 2. When was your first experience with TAVI?
Prompt: How many of them have you done since then?
 3. What are the criteria for patients to be selected as candidates for this procedure?
Prompt for: age/comorbidities/previous interventions/degree of stenosis
 4. In your experience, at what point in the patient's care are patients referred for TAVI?
 5. Could you draw the clinical pathway used for patients with severe AS symptoms, including the tests, to determine whether they are suitable for TAVI?
Prompt for: whether via general practitioner (GP)/emergency medical services (EMS)/ or any other means
 6. Are there further tests that you think should be requested before the patient undergoes this procedure?
 7. Who decides when the patient becomes a candidate for TAVI?
Prompt for: Is it done by a team?
 8. How would you describe the intraoperative risks of this procedure?
Prompt for: patients/family members/colleagues
 9. In your experience, how long do patients stay in hospital after TAVI?
 10. How long do you follow up with your patients once they leave the hospital?
Prompt for possible further tests (e.g. 30 days/six months/one year)
 11. What formal training on TAVI is currently available?
Prompt for cardiologists, multidisciplinary team and timeframe
 12. What role do you think TAVI will play in the future of cardiac care?
-

Chapter 3. Results

3.1 Literature search

The bibliographic database searches identified a total of 7,550 citations. Once duplicates were removed, 4,156 unique references remained. Of these, 3,713 were excluded after screening the titles and abstracts, and 443 potentially relevant publications were assessed for full text review. The manual scanning of reference lists, grey literature searching and PubMed update alerts retrieved 14 additional studies, including several health technology assessments on transcatheter aortic valve implantation (TAVI).¹¹²⁻¹¹⁵ The search and study selection process for clinical studies is shown in the PRISMA flow diagram in Appendix B, Figure 12.⁹⁸

Ultimately, 115 potentially relevant studies were selected for appraisal and data extraction. After undertaking a third detailed screening evaluation, 61 were excluded - mainly because data on the same patients were reported in multiple publications with different follow-up periods. Excluded publications, along with reasons for exclusion, are listed in Appendix B, Table 7. In total, 56 reports, published from 2009 to 2013, met the inclusion criteria for appraisal and data extraction. Of these, 37 studies reported clinical outcomes, 14 reported health-related quality of life and five studies specifically assessed the learning curve for performing TAVI. Disagreements regarding the inclusion criteria were resolved through consensus.

3.2 Characteristics and quality of clinical studies

In Appendix D, Table 11 gives general descriptions and characteristics of 37 experimental or observational clinical studies, including seven comparative studies.^{30,31,116-120} The experimental studies consisted of two randomized controlled trials (RCTs) and two analyses that reported on longer follow-up data for each of the original trials.

The observational studies consisted of one non-randomized controlled trial, two cohort studies and 30 case series, of which one study reported longer follow-up data for the original study.¹²¹ All but two studies reported the patient enrollment period, which ranged from May 2005 to October 2011. The 37 studies represent 10,500 TAVI patients for the present analyses, with a number of patients ranging from 10 to 2,361 in the TF

group, and from 22 to 975 in the TA group. Overall, TF and TA groups consisted of 6,466 (61.6%) and 4,034 patients (38.4%), respectively.

One study provided data for a group of patients with moderate surgical risk; this group was therefore excluded from the current analysis.¹²² In another study, Webb et al., (2009), the TA group overlapped with TA patients of the Ye et al. (2010) study; consequently, the TA group of Webb et al. was excluded from the analysis.^{123,124}

Only one clinical study used a health-related quality of life (HRQoL) measurement: the Minnesota Living with Heart Failure Questionnaire which is used to measure the impact of heart disease on patient quality of life.¹²⁵ Most studies did not report the type of medical treatment provided to patients after the TAVI intervention.

Twenty five studies provided definitions for complications after TAVI. Of these, eight studies used the VARC,^{118,125-131} one study used VARC consensus only to define procedural success and 30-day mortality;¹³² and both randomized controlled trials (RCTs) and one case series used a modified version of VARC definitions.^{30,116,133} The other 13 studies provided definitions either from their own study protocol or referred to different sources,^{120,122,123,134-143} and nine studies provided no definitions.^{110,119,124,144-149}

Follow-up periods to capture clinical complications ranged from 30 days to three years:

- 26 studies reported 30-day time interval^{118,120,123-125,127,128,130-132,134-149}
- Seven studies reported one-year follow-up^{30,116,119,121,126,129,133}
- Three studies reported two-year follow-up^{31,117,122}
- One study reported three-year follow up.¹²⁶

For most complications, only two comparative studies provided complication rates at one and two-year follow-up, thereby limiting accurate measurement of the effectiveness of TAVI.

In some studies, the authors combined data from other approaches with the transfemoral approach. For instance, data pertaining to subclavian (SC) approaches were combined with data from the TF approach with a proportion ranging from 1.9% to 7.4% in 10 observational studies.^{118,125-128,130,135,137,139,144} One of these studies also included five TAO and 26 TA approaches combined with the TF approach (0.05% and 4%

respectively).¹³⁵ In some studies, a small number of other approaches (e.g., trans-subclavian) were combined with data on TF approaches. In general, this thesis uses the term “groups” rather than “approaches” to indicate this possible variation.

While four studies provided no inclusion criteria,^{118,120,134,134} 19 studies provided at least one parameter or a specific comorbidity as inclusion criteria (e.g., STS score, aortic valve area or porcelain aorta).^{122,124-126,129,130,132,133,135,137,139,141,143,145-148} Eleven studies reported inclusion with no parameters (i.e., excessive surgical risk, inoperable patients)^{110,123,127,128,131,136,138,140,142,144,149} (Appendix D, Table 9).

3.2.1 Comparative studies

The seven comparative studies of TAVI are shown in Table 5 below. These include two RCTs and the two follow-up studies to these trials, as well as one non-randomized controlled trial and two cohort studies.

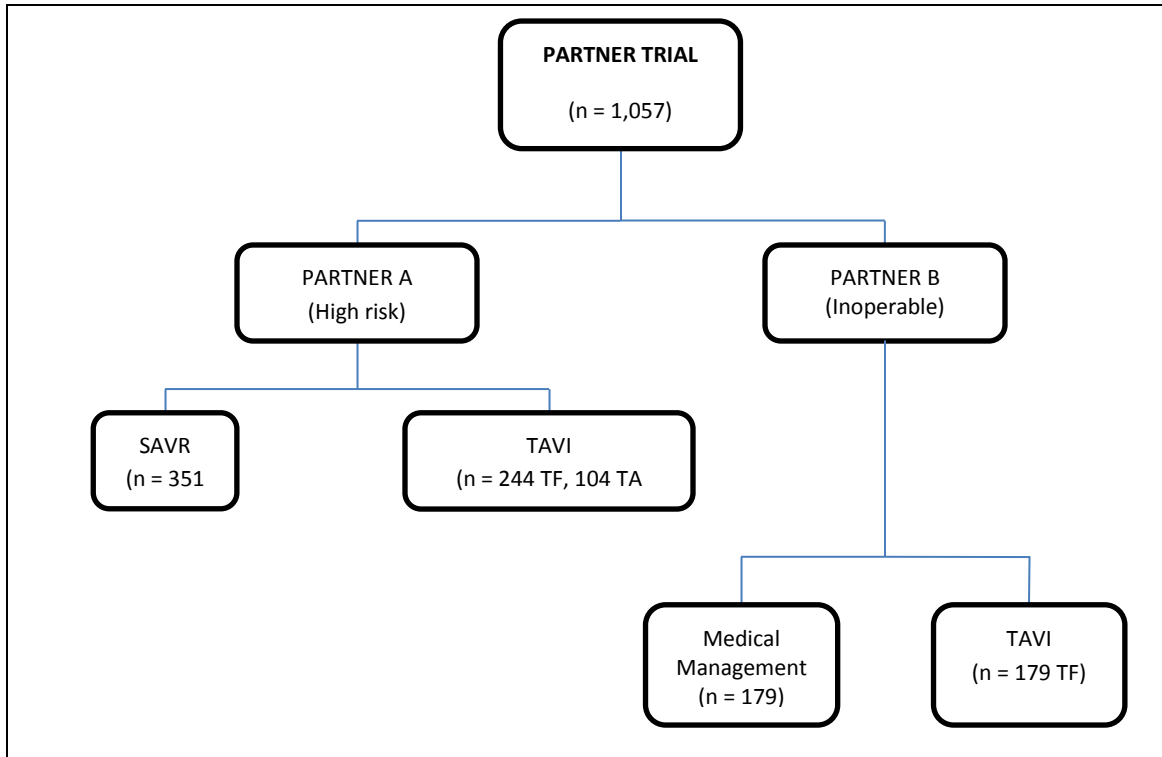
Randomized controlled trials (RCTs)

Both RCTs that enrolled patients with severe symptomatic aortic stenosis are shown in Figure 5. They are part of the Placement of Aortic Transcatheter Valve (PARTNER) Trial to assess the safety and efficacy of the Edwards SAPIEN valve. According to the overall study design, 3,105 patients were screened and subsequently 1,057 patients were divided into two groups categorized as “high risk” (PARTNER A) or “inoperable,” (PARTNER B) thereby forming two RCTs.

In the first group, 699 high risk patients were randomly assigned to either TF or TA procedure depending on whether the patient’s peripheral arteries could accommodate the size of sheath required (22 French for the 23-mm valve and 24 French for the 26-mm valve), versus SAVR. Patients in the surgical arm were stratified according to whether a TF or TA approach would have been performed if TAVI had been assigned.¹¹⁷ In the second group, 358 patients with the possibility of transfemoral access were randomly assigned to compare the TAVI procedure using the TF approach to medical management (MM). To qualify, the included patients had to be considered as inoperable by at least two heart surgeons, either because of clinical or anatomical factors. In addition to medication, most patients in the medically managed arm (84%)

also underwent balloon aortic valvuloplasty (BAV), a procedure that widens a narrowed heart valve with a balloon.

Figure 5. Partner Trial Design



Abbreviations: MM, medical management; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral

While intention-to-treat analysis was consistently performed in both RCTs, (i.e., analysis based on the intervention to which patients were originally allocated), only data per-protocol analysis (i.e., including only those patients who completed the treatment originally allocated)¹⁵⁰ was reported for echocardiographic measurements. The clinical status of TAVI patients was assessed using the New York Heart Association (NYHA) functional classification scale.

These RCTs were conducted in 25 centres (21 in the United States, three in Canada and one in Germany) and were followed by two analyses that reported two-year follow up data for each of the original trials. More details on the studies are presented in Appendix D, Table 11.

Non-randomized controlled trials and cohort studies

The other comparative studies consisted of one non-randomised trial (NRT) and two cohort studies. The NRT was a multicentre study that involved 358 patients referred for TAVI who were allocated according to treatment group (TAVI, SAVR, MM). Allocation was not properly controlled as TAVI could be declined in favour of either SAVR or MM, primarily based on patient preference, thereby introducing the risk of selection bias.¹¹⁸ In addition, an unequal number of patients were assigned to each treatment arm (n = 228 TF and 7 SC¹ versus 24 SAVR), thereby decreasing the power to detect statistically significant differences between the groups. With regard to the MM group (n = 99), outcomes were reported as “beyond 30 days” comparing the number of deceased patients in this group to the number of deceased patients in the TAVI (TF and TA) and SAVR groups.¹¹⁸ As the time interval was not specified, this data was not included in the analysis.

Of the cohort studies, the first by Zierer et al., was a retrospective matched cohort study which compared TA patients to SAVR patients. The authors declared the final allocation decision was “mainly based on patient’s preference,” thereby introducing the risk of bias. No information was provided on attempts to adjust for potential confounders.¹¹⁹

The second cohort study attempted to account for baseline differences by using propensity score matching techniques to adjust for confounding. This technique enables both groups (treated and untreated) to become similar by distributing possible predicted variables at baseline.¹⁵¹ However, the authors acknowledged that their early experience with TAVI may have underestimated its benefits due to the learning curve for the procedure (i.e., because of the small numbers of patients involved: 10 in the TF group, and 30 in the TA group).¹²⁰

The three observational studies reported no information on the functional improvement of TAVI patients, which is usually assessed by means of the New York Heart Association (NYHA) functional scale. In addition, the papers by Nuis et al. and Johansson et al. did not report echocardiographic findings or patient enrollment criteria.^{118,120}

¹ The subclavian data was combined with the transfemoral data

Table 5. Comparative studies				
Study	Study design	TAVI (n)	Patient allocation	Control group (n)
Smith et al. 2011 ¹¹⁶ Kodali et al. 2012 ¹¹⁷	Open label RCT	244 TF 104 TA	Patients allocated by means of computer-generated randomized blocks	358 SAVR
Leon et al. 2010; ³⁰ Makkar et al. 2012 ³¹	Open label RCT	179 TF	Same as above	179 MM*
Nuis et al. 2012 ¹¹⁸	NRT	228 TF	TAVI patients were allocated to SAVR according to: - Patient preference (29%) - Peripheral vascular disease (13%) - Non-severe AS (11%)	24 SAVR
Zierer et al. 2009 ¹¹⁹	Retrospective matched cohort study	21 TA	Patients who underwent TAVI were matched to SAVR according to morbidity and mortality	30 SAVR
Johansson et al. 2011 ¹²⁰	Retrospective matched cohort study	10 TF 30 TA	SAVR patients were compared to TAVI patients by means of propensity score-matching	40 SAVR

* Balloon aortic valvuloplasty (BAV) was performed in 83% of patients.

Abbreviations: n, number of patients; SAVR, surgical aortic valve replacement; MM, medical management; RCT, randomized controlled trial; NRT, non-randomized trial; TF, transfemoral; TA, transapical; TAVI, transcatheter aortic valve implantation;

Case series

The other 30 studies were case series: 18 single-centre and 12 multicentre studies. Of these, eight were registry studies, including one that reported one-year follow-up data for the original 30-day study.^{121,140} The studies were mainly conducted in Europe (n = 23), with four in Canada, one in the United States, one in Israel, and one in Brazil. Twenty studies reported echocardiographic findings and 10 reported on the distribution of patients per NYHA functional classification scale. Of the 30 case series, 10 were small (ranging from 22 to 77 patients per study), making it difficult to draw conclusions on reported complications.^{122,124,127,128,136,138,143,144,147,148} In two studies, the authors explicitly excluded patients from the analysis who died during the procedure – which may have introduced the risk of bias.^{110,125}

3.2.2 Studies according to type of TAVI valve

As illustrated in Appendix D, Table 11, most of the clinical studies (n = 19) exclusively used Edwards SAPIEN valves (involving 1,256 TF and 3,303 TA approaches). In one of these studies, the authors reported the use of Cribier-Edwards valves “early in the series” representing a minority of procedures with no further information; the data was combined with that for SAPIEN and SAPIEN XT valves.¹²³ No studies reported exclusive use of the Sapien XT (3rd generation) valve in either the TF or TA patient groups. However, four studies reported the use of SAPIEN XT combined with the SAPIEN valve.^{123,129,135,142} One of these studies also included patients who received the Cribier-Edwards (n = 57 (16.8%)) combined with SAPIEN (n = 275 (81.1%)) or SAPIEN XT (n = 7 (2.1%)) valve implantation.¹⁴² The patient-valve details were identified through another peer-reviewed study that was excluded due to patient overlap.¹⁵² Six studies used both the balloon-expandable Edwards SAPIEN valve and the self-expandable CoreValve prosthesis, representing approximately 2,063 and 2,062 transfemoral approaches, respectively.^{110,129,130,134,135,139} Ten studies used exclusively the CoreValve prosthesis representing approximately 1,051 TF implantations.^{118,122,125-128,131,136,137,144} The Edwards SAPIEN valve was used in all TA implantations except in five patients of a case series study where the CoreValve prosthesis was used as part of their research protocol.¹¹⁰ Most of the procedures used either the second generation SAPIEN valve or the 18 Fr third generation CoreValve devices.

3.3 Patient characteristics

Table 12, in Appendix D, provides details on demographic baseline characteristics. All patients had severe symptomatic AS according to the American College of Cardiology and the American Heart Association guidelines (described in Chapter 1). These patients were considered “inoperable” “not suitable for surgery” or at “high risk” for surgery. The mean age of all patients undergoing TAVI was 81.6 ± 7.2 years, and all but one study reported gender distribution.¹²⁵ Based on the pooled average, there was a statistical significant difference in the proportion of females (n = 5,455) compared to males (n = 4,956) who underwent TAVI, (52.4% vs 47.6%; $p < 0.001$).

Operative mortality risk was assessed using either The Society of Thoracic Surgeons Predicted Risk Evaluation (STS) score (range 0% to 100%), with higher scores of $\geq 10\%$,

denoting greater surgical risk, and/or the logistic European System for Cardiac Operative Risk Evaluation (logistic EuroSCORE), which reflects higher predicted mortality (range 0 to 100%), with higher scores of $\geq 20\%$ denoting greater surgical risk. Both methods are used to determine the predicted operative mortality risk for patients undergoing cardiac surgery, but not for the subset of patients who are referred for TAVI. For instance, both risk scores have limitations in identifying a number of comorbidities such as chest wall radiation, compromised respiratory function, frailty and porcelain aorta.^{128,153}

To make comparisons with other data less difficult, Zahn et al. recommend the use of both the logistic EuroSCORE and the STS score per study protocol¹³⁵ Similarly, when comparing patients who underwent TAVI to those who underwent SAVR and/or MM, no significant difference is expected between TAVI and control groups.¹⁵⁴

Most clinical studies (n = 22) used both assessment scores at baseline, 11 studies used only the EuroSCORE and one study used only the STS score. Since 12 studies did not evaluate patients by using both risk scores, caution must be used when interpreting patient comorbidities at baseline.

Of the studies that reported the STS score, the pooled mean total was $9.4\% \pm 11\%$ for patients in the TF group (n = 4,156), and $11.5\% \pm 11.3\%$ for patients in the TA group (n = 3,245), with a significant difference between groups ($p < 0.001$). Similarly, of the studies that reported the logistic EuroSCORE, the pooled mean total was significantly higher for the patients who were treated with TA (n = 3,800) compared to the TF group (n = 5,573), ($27.9\% \pm 16.3\%$ vs $22.6\% \pm 14.7\%$; $p < 0.001$). These EuroSCORE results are in line with the study by Thomas et al. (n = 1,038) which observed a significantly higher risk profile based on the EuroSCORE results for the TA than the TF group, indicating that the comparison of these two patient categories may not be valid.^{121,140}

In comparison, when patients who underwent either TAVI (TF and TA) were compared (Smith et al.,¹¹⁶ n = 699) no statistical differences were found in the STS scores (11.7 ± 3.3 vs 11.8 ± 3.5 ; $p = 0.70$)^a or EuroSCORE (29.1 ± 16.1 vs 29.8 ± 15.9 ; $p = 0.93$).^a

Comparisons of patients who underwent either TF or TA with SAVR or MM, according to their respective risk scores are summarized in Table 13 and Table 14. However, in Leon

^a p value obtained from Smith et al. Supplementary Appendix

et al.,³⁰ unlike the STS score, the Logistic EuroSCORE shows a significant difference in patient comorbidities at baseline between TAVI and MM.

3.4 Quality assessment

Appendix D, Table 11 shows all clinical studies graded according to the Oxford Centre for Evidence-based Medicine (CEBM) levels of evidence, which grades each study based on design and methodological rigour from level 1a (highest) to level 5 (lowest).¹⁰⁰ The experimental studies were graded as level 1b, and all the 33 observational studies were graded as level 4 (low quality evidence). The table below shows results of the risk of bias analysis for both RCT studies (Table 6).⁹⁷

Table 6. Risk of bias assessment of the two TAVI RCTs		
Entry	Judgement	Support for judgement
Leon et al. 2010 ³⁰ (PARTNER B)		
Random sequence generation (selection bias)	Low Risk	Quote: "patients were randomly allocated." Comment: "Computer-generated scheme, blocked separately at each participating site and for each of the trial cohorts."
Allocation concealment (selection bias)	Unclear	Quote: "...Not clearly reported by authors." Comment: Probably not done.
Blinding of participants and personnel (performance bias)	High risk	Quote: "Double blinding obviously unethical in this type of study." Comment: Not done.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	High risk	Quote: "not double-blind." Comment: Not done.
Blinding of outcome assessment (detection bias) (mortality)	Low risk	Quote: "Primary endpoint was death." Comment: Such outcome measurement is not likely to be influenced by the lack of blinding.
Incomplete outcome data addressed (attrition bias) (short-term outcomes (two to six weeks))	Low risk	No missing data reported, six patients in standard treatment group withdrew.
Incomplete outcome data addressed (attrition bias) (longer-term outcomes (> six weeks))	Low risk	No missing data reported.
Selective reporting (reporting bias)	Low risk	Study protocol is available and pre-specified outcomes have been reported.

Table 6. Risk of bias assessment of the two TAVI RCTs		
Entry	Judgement	Support for judgement
Free of other bias?	High risk	The fact that several investigators revealed travel reimbursement and grant support from Edwards Lifesciences raises concerns. Moreover, baseline differences between both groups indicated that TAVI had a lower overall risk than MM (e.g. COPD and atrium fibrillation).
Smith et al. 2011¹¹⁶ (PARTNER A)		
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned." Comment: "Computer-generated scheme, blocked separately at each participating site and for each of the trial cohorts."
Allocation concealment (selection bias)	Unclear	Quote: "...not reported by authors." Comment: Probably not done.
Blinding of participants and personnel (performance bias)	High risk	Quote: "Double blinding obviously unethical in this type of study." Comment: Not done.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	High risk	Quote: "not double-blind" Comment: Not done.
Blinding of outcome assessment (detection bias) (mortality)	Low risk	Quote: "Primary endpoint was death." Comment: Outcome measure is not likely to be influenced by the lack of blinding.
Incomplete outcome data addressed (attrition bias) (short-term outcomes (two to six weeks))	Low risk	No missing outcome data registered.
Incomplete outcome data addressed (attrition bias) (longer-term outcomes (> six weeks))	Low risk	No missing outcome data registered.
Selective reporting (reporting bias)	Low risk	Study protocol is available and pre-specified outcomes have been reported.
Free of other bias?	Not clear	The fact that several investigators revealed travel reimbursement and grant support from Edwards Lifesciences raises concerns. Additionally, baseline differences between both groups indicated that TAVI had a lower overall risk than MM (e.g. COPD ¹ and atrium fibrillation)

3.5 Assessment of feasibility

An accurate comparison of procedural success rates among studies was difficult owing to the inconsistent definition of "procedural success" in different studies (Table 10). For

¹ COPD, chronic obstructive pulmonary disease

instance, two studies used the definition “no perioperative mortality” for procedural success, and five studies used VARC definition.¹⁰²

One study defined procedural success as “the non-occurrence of major cardiac and cerebrovascular adverse events (MACCE) during the first 48 hours,”¹²² while the other measured MACCE over the entire hospital stay (> 72 hours), resulting in a procedural success rate of 72% due to its conservative definition of procedural success.¹²² Therefore, this study was not included in the pooled analysis. Owing to the inconsistency of the definitions of procedural success, where possible, procedural success was recalculated using the definition applied in this analysis (see section 2.5 Outcome measures).

Feasibility outcomes, including procedural success, valve-in-valve and conversion to SAVR are shown in Table 15.

3.5.1 Procedural success

The pooled average rate in 19 studies that enrolled 4,995 patients in the TF group and 2,361 in the TA group was not significantly different (96.5% vs 95.6%; $p = 0.06$).

3.5.2 Valve-in-valve implantation

In 19 studies that enrolled 7,218 patients (4,601 TF and 2,617 TA), the occurrence of a second valve implantation was significantly higher in the TA than in the TF group: (2.7% vs 1.9%; $p = 0.02$). The main reasons for a second valve implantation were valve embolization, regurgitation, and malpositioning.^{116,125,127,142,145,146} One study reported that two patients had their TF procedure aborted due to vascular complications. These two patients underwent a successful TA procedure five months thereafter.¹⁴³ Two studies suggested that valve-in-valve complication could be attributed to the learning curve.^{127,145}

3.5.3 Conversion to SAVR

Twenty five studies that enrolled 8,147 patients (5,491 TF and 2,656 TA) reported conversion to SAVR which was significantly higher in the TA than in the TF group: (1.78% vs 0.71%; $p < 0.0001$). The reasons for conversion to SAVR included inadequate placement of the aortic valve within the aortic annulus, valve embolization and migration, root rupture and severe aortic regurgitation.^{132,136,142} Because the TA approach is not as widely used as the TF approach, it is possible this finding could either

reflect the learning curve in TA implantation or that patient comorbidities were not captured by the preoperative variables.¹⁵⁵

3.5.4 Operative outcomes

Operative outcomes included procedural time, length of intensive care or cardiac care unit stay (ICU) and length of hospital stay (Appendix D, Table 16).

Procedural time

Twelve studies reported the mean procedural time comprising 1,384 patients in the TF group, and 474 patients in the TA group. Because it requires a small surgery, the TA intervention was longer (116.3 ± 53 minutes) than the TF intervention (77.2 ± 41 minutes).

Length of intensive care unit stay (ICU)

Three studies comprising 81 patients reported the mean intensive care unit (ICU) stay. In the TA group, the pooled average was 2.5 ± 2.7 days.^{116,119,148} In the TF group, both studies, Zahn et al.¹³⁵ and D’Onofrio et al.,¹⁵⁶ reported the same median ICU stay of two days (interquartile range one to three days). For SAVR, Zierer et al.¹¹⁹ reported a significant difference in length of stay between TA and SAVR groups (1.0 ± 0.4 days vs 3.2 ± 1.9 days; $p < 0.001$).ⁱⁱ

Length of hospital stay (without ICU)

Only studies that reported the mean ICU and hospital stay associated with a single group or studies that reported hospital data associated with TF and TA groups separately were included in the statistical analysis. This was intended to decrease the risk of bias where length of hospital stay may have included length of ICU stay.¹⁵⁷ Under this criteria, five studies reported a mean length of hospital stay associated with both groups; the overall mean length of hospital stay for patients in the TF group ($n = 2,385$) was significantly shorter than for patients in the TA group ($n = 724$): (9.1 ± 8.1 days vs 10.7 ± 8.1 days; $p < 0.001$).

ⁱⁱ p value obtained from Zierer et al., 2009¹¹⁹

3.6 Assessment of safety/effectiveness

3.6.1 Periprocedural mortality at day-three follow-up

The periprocedural (or perioperative) mortality (Table 17) of the TF and TA groups was reported in 21 studies comprising 1,573 and 667 patients, respectively. There was no significant difference between these two groups (2.4% vs 3.0%; $p = 0.3$). Of these studies, four provided no information on cause of death,^{30,125,139,142} and four studies reported zero periprocedural mortality.^{120,137,138,147} Of note, although this finding suggests that the difference could have happened by chance ($p > 0.05$), there may still be a clinical significance that is not measured by statistical test.

Vascular complications were the most commonly reported cause of periprocedural death. The rate of this event was based on the analysis of 921 patients in the TF group and 419 patients in the TA group. This event occurred more significantly in the TF than in the TA group (2.3% vs 0.5%; $p = 0.02$). Other complications that led to death occurred rarely in both groups across studies, such as heart or multi-organ failure 0.42% and 1.3% reported by Nuis et al.¹¹⁸ and Sinning et al.¹³⁶ in the TF group and 1.4% and 2.6% reported in the TA group by Ye et al. and Nielsen et al.,^{124,149} respectively (Table 17). Bleiziffer et al. discussed the relationship between survival and clinical experience and indicated that some of the mortality after TAVI could be attributed to the learning curve.¹¹⁰

In the comparative studies, Smith et al. 2011¹¹⁶ reported a greater rate of death when TAVI procedures (TF and TA combined) were compared to SAVR, but the difference was not statistically significant (0.9% vs 0.3%; $p = 0.3^a$). Other results for periprocedural mortality in comparative studies are summarized in Table 18. The only study that reported this finding, Zierer et al.,¹¹⁹ found there was no statistical difference between the TA and SAVR control group.

^a p value obtained from Smith et al., 2011, Supplementary Appendix

3.6.2 Mortality at 30 days

Mortality was subdivided into three categories:

- 1) All-cause mortality, although objective, does not distinguish events directly related to the heart or to the TAVI procedure¹⁰²
- 2) Cardiac mortality, which are events associated with the heart, TAVI procedure or the treatment device¹⁰²
- 3) Non-cardiac mortality, which are events not directly related to the heart, TAVI procedure or the treatment device

Non-cardiac mortality was not explicitly reported; terms such as “all-cause and cardiac,” “30-day mortality” or “all-causes of death” were more commonly used across studies.

All-cause and cardiac mortality

Table 19 shows all-cause mortality, cardiac and relative causes. All-cause mortality was the most widely reported outcome based on 6,466 patients in the TF group and 4,034 patients in the TA group in 34 studies. Of these, seven studies comprising 1,846 patients in the TF group and 1,223 patients in the TA group reported mortality based on all-cause only. At one month, the pooled average of all-cause mortality was higher in the TA than in the TF group (9.5% vs 8.6%; $p = 0.08$), but the difference was not statistically significant.

Five studies reported cardiac-mortality without providing their specific causes.^{116,122,129,130,145} In 27 studies representing 6,470 patients, the pooled average rate of cardiac mortality was higher in the TA ($n = 2,236$) than the TF group ($n = 4,234$), but the difference was not statistically significant (6.3% vs 5.7%; $p = 0.3$). This result was similar to that of Smith et al.¹¹⁶ for the TA ($n = 104$) and TF ($n = 244$) procedures, where there was no significant difference with regard to all-cause and cardiac mortalities (3.8% vs 3.3%; $p = 0.8$ and 2.9% vs 3.3%; $p = 1.0$, respectively) (see Table 21).

Of all cardiac deaths, vascular complications, including cardiac tamponade, vascular dissection or perforation, and bleeding, were the most commonly reported cause of death. Based on 1,323 patients in the TF and 1,223 of the TA group, the pooled average

rate of vascular complication was higher in the TF than the TA group (2.1% vs 0.7%, $p < 0.01$). In contrast, cardiac or multi-organ failure was the most frequently reported cause of death with the rate higher in the TA ($n = 1,223$) than in the TF group ($n = 1,120$), but the difference was not statistically significant (3.2% vs 2.4%; $p = 0.26$).

Across 2,573 patients, the rate of valve-related deaths was significantly higher in the TF group ($n = 1,350$) than in the TA group ($n = 1,223$), (1.2% vs 0.3%; $p = 0.01$); Bleiziffer et al. ($n = 203$) indicated that because the TA approach, unlike the TF approach, does not manipulate the aortic arch with large catheters the risk of valve related complications could be significantly reduced.¹¹⁰

In one large registry, Thomas et al. ($n = 1,038$) reported that more than half of deaths during the first 30 days in both groups were attributed to cardiac and multi-organ failure. Although the authors observed an association between high risk EuroSCOREs (e.g., 30 to 35) and 30-day mortality, the reasons that led to cardiac and multi-organ failure in both groups remained unclear.¹⁴⁰ Of note, there were no reports of death due to endocarditis at 30-day follow-up.

Non-cardiac mortality

The causes of non-cardiac deaths after TAVI are shown in Table 20. The rate of this event was based on analysis of 2,236 patients in the TA and 4,157 patients in the TF group. The pooled average was higher in the TA than in the TF group, (3.1% vs 2.7%; $p = 0.4$), but the difference was not statistically significant. The most commonly reported non-cardiac cause of death was stroke. The rate was more significant in the TF ($n = 1,170$) than the TA group ($n = 1,515$), (1.2% vs 0.5%; $p = 0.04$).

The rate of infection or sepsis was the second most commonly reported cause of death, followed by respiratory causes. There was no statistically significant difference in the rate of either between the two groups.

Since cardiac and non-cardiac mortality were only recalculated where possible (i.e., according to the definition provided in this analysis), caution must be applied when

interpreting results. A summary of all causes, cardiac and non-cardiac deaths, in comparative studies, is shown in Table 21.

3.6.3 Mortality at one year

All cause/cardiac and non-cardiac mortality along with their causes are illustrated in Table 22 and Table 23.

TF versus TA group analysis

Five studies that collectively enrolled 806 patients (681 TF and 125 TA), reported mortality data based on the three categories previously described. The occurrence of all-cause and cardiac mortality was higher in the TA than the TF group (28.2% vs 27.6%; $p = 0.7$) and (18.2% vs 13.2%; $p = 0.12$) and the occurrence of non-cardiac mortality, was higher in the TF than the TA group (14.2% vs 9.5%; $p = 0.26$), but none of these reached statistical significance.

Within-group comparison for cardiac and non-cardiac mortality

This analysis was performed to examine the rate of all cause, cardiac (procedural or valve related) and non-cardiac mortality within the same TAVI group at one-year follow-up.

In the TF group, the pooled estimate for all-cause mortality was significantly higher than the cardiac mortality (27.5% vs 13%; $p < 0.001$). However, there were no statistically significant differences in the rates of non-cardiac and cardiac mortality.

In the TA group, the pooled estimate for all-cause mortality was not significantly higher than the cardiac mortality (28.1% vs 18.2%; $p = 0.07$), whereas cardiac mortality was significant higher compared to non-cardiac mortality (18.2% vs 9.5%; $p = 0.04$).

Of note, since the causes of cardiac and non-cardiac deaths were not reported by Smith et al., it is likely that these results could have been different had they been recalculated according to the collapsed definitions of the present analysis (see Appendix C, Table 8).

Comparative studies versus MM or SAVR

Table 24 shows that all cause and cardiac mortality in Leon et al.³⁰ demonstrated that the TF approach could be significantly more beneficial than medically managed therapy (including BAV) in patients not suitable to undergo SAVR. In Smith et al.,¹¹⁶ cardiovascular mortality was higher but did not reach statistical significance in both TAVI approaches compared to SAVR, $p = \text{NS}$.ⁱⁱⁱ In the TA group of Zierer et al.,¹¹⁹ the only two causes of death reported were due to pulmonary hypertension and pneumonia, whereas in the SAVR group, the only two reported causes of death were due to cardiac causes (heart failure and sudden death).

Mortality and causes of death within the TF group

With the exception of Smith et al.,¹¹⁶ the other three studies^{30,126,136} reported mortality with causes of deaths (cardiac/non-cardiac) at one-year follow-up over 437 patients who received the TF implantation. All-cause mortality was significantly higher compared to cardiac mortality (28.5% vs 11.4%; $p = 0.015$), whereas non-cardiac mortality was significantly higher than cardiac mortality (17.1% vs 11.4%; $p = 0.02$). The major causes of non-cardiac deaths were respiratory causes (7.8%), renal failure (3.0%), infection or sepsis (2.5%), stroke (2.0%), cancer (1.7%), and bleeding aneurysm (1.4%). For cardiac causes, heart failure or multiple organ failure were the most commonly reported cause of death (5.1%), followed by sudden death, myocardial infarction and endocarditis (0.9%, 0.48% and 0.45% respectively).

No pooling in the TA group was possible, as only one study, Zierer et al.,¹¹⁹ reported causes of death at one-year follow-up.

Non-cumulative mortality from 30 days to one year

In the RCT with inoperable patients, most deaths in both groups occurred between 30 days and one year; this trial clearly demonstrated the benefits of TAVI over MM with a 22.4% difference in mortality between the two groups. In Smith et al.,¹¹⁶ the cardiac mortality was not statistically significantly different between the two groups. Similarly, there was no significant difference in mortality between TAVI and controls across all comparative studies between 30 days and one year (Table 25).

ⁱⁱⁱ Data obtained from Supplementary Appendix of Smith et al., 2011¹¹⁶

Non-specific reports

The study by Thomas et al.,¹²¹ with 1,038 participants, did not specify the approach used (TF or TA), and reported 17.2% for all-cause mortality from 30 days to one year (179/1038). The cardiac causes (4.3%; n = 45) combined with unknown causes (4.4%; n = 46) indicated that cardiac and non-cardiac mortality were similar between these two groups (8.7% vs 8.4%). This study also reported heart failure as the most common cause of cardiac death 2.7% (28/1,038) followed by sudden death 1.7% (18/1038), MI (0.6%) and death with endocarditis (0.3%). Respiratory causes (2%), renal failure (1.1%), cancer (1.0%) and stroke (0.9%) were among the most common non-cardiac deaths. However, these results (i.e., the combined approaches) should be interpreted with caution as the same study highlights a statistically significant difference in underlying comorbidities between the two groups as measured by the logistic EuroSCORE, which was much higher for the TA group compared to TF group (29.1% versus 25.7%; p<0.001).¹²¹

The Moat et al. study,¹³⁴ with 599 patients in the TF group, reported only all-cause death (18.5%) with a logistic EuroSCORE of 17.1%. In the studies that reported cause of death following the TA approach with longer than 30-day follow-up, it was impossible to associate patients with a specific time interval since the authors referred to any mortality after 30 days as “during the follow-up interval up to 487 days (range three months to four years)”¹⁴⁵ “late clinical outcomes,”¹²⁴ or simply “late mortality.”¹³²

Nonetheless, it was possible to observe a similar trend associated with the causes of death after 30 days which were mainly non-cardiac related. For instance, in Walther et al.¹⁴⁵ (n = 299), which refers to longer term follow up as “during the follow-up interval,” all-cause mortality was 28% (84/299). Of these, respiratory causes (6%), sepsis (5.3%), and stroke (1%) were the most common non-cardiac deaths. Heart failure and multi-organ failure^{iv} accounted for more than 9.0% of cardiac deaths (29/299) followed by cancer (1%).

Ye et al.¹²⁴ (n = 71), reported that 59 patients survived beyond 30 days with 10 deaths thereafter. Most non-cardiac deaths were attributed to chronic obstructive pulmonary

^{iv} Data reported combined with sepsis

disease (n = 4) followed by cancer (n = 1) and gastrointestinal bleeding (n = 1), whereas cardiac-deaths were attributed to chronic heart failure, multi-organ failure (n = 3), followed by myocardial infarction (n = 1).

D'Onofrio et al.¹³² (n = 504) reported the death of 34 patients during "late mortality" (9.2 ± 6.5 months) as follows: congestive heart-failure as the most common cardiac death (n = 12), followed by sudden death (n = 5). Among the non-cardiac deaths, sepsis or respiratory was the most common cause (n = 8), followed by stroke (n = 5), cancer (n = 3) and cirrhosis (n = 1).

3.6.4 Mortality at two years

No clinical studies reported causes of death at two-year follow-up (Table 26). The pooled analysis of all-cause, cardiac and non-cardiac mortalities of the three studies, which represented 495 patients in the TF group and 104 patients in the TA group were reported at two-year follow-up. To maintain consistency, the same criterion of pooling actual data as previously described was applied. Makkar et al.³¹ and Kodali et al.¹¹⁷ were also included since the difference between the actual number of events with the censored data (e.g., missing data on withdrawals and patients lost to follow-up) was not statistically significant.

TF versus TA group analysis

No significant differences in all-causes, cardiac and non-cardiac mortalities were found between the TF and TA groups, (37.5% vs 41.1%; p = 0.59), (24.7% vs 26%; p = 0.73) and (14% vs 15%; p = 0.37), respectively. In the high risk patient RCT, cardiac and non-cardiac mortalities were more frequent in the TA than the TF group (26.0% vs 19.6%; p = 0.2) and (15.1% vs 11.3%; p = 0.3), but the difference was not statistically significant.

Within-group comparison cardiac and non-cardiac mortality

The pooled estimate for cardiac mortality was significantly higher than non-cardiac mortality in the TF group, (24.6% vs 13.9%; p < 0.001). In contrast, cardiac mortality in

the TA group in the single arm of the high risk patient RCT¹¹⁷ (n = 104) was higher than non-cardiac mortality (26% vs 15.1%; p = 0.06), but without statistical significance.

TF and TA groups versus control

In the inoperable-patient RCT, at two-years of follow-up, all-cause and cardiac mortality were significantly higher in the MM than in the TAVI groups (p < 0.001), whereas the occurrence of non-cardiac mortality was not significantly different between the two groups. In contrast, there were no significant differences in mortality from all causes, cardiac or non-cardiac mortality in the high risk RCT (Table 27).

Non-cumulative mortality between one and two years

In Leon et al., the mortality rate in the MM group was higher than in the TF group (8.2% vs 3.7%; p = 0.07), but the difference was not statistically significant.³¹ Overall, no comparative study showed a significant difference between TAVI and controls at 1 and 2-years of follow-up (Table 25).

Non-specific reports

One registry study, Moat et al.,¹³⁴ (n = 870) reported only all-cause death for patients in the TF group 135/599 (22.5%) at two-years of follow-up.

3.6.5 Mortality at three years

Only one observational study, Ussia et al., 2012,¹⁵⁸ reported causes of death at three-years of follow-up (Table 29). Based on the current analysis endpoint definitions, cardiac deaths occurred in 15 patients (8.2%) and non-cardiac deaths in 47 patients (26%). Heart failure occurred in 11 patients (6.1%) and represented the major cause of death among cardiac causes, while respiratory causes, as the major overall cause, accounted for 13 patients (7.2%) among non-cardiac deaths.

3.7 Complications

3.7.1 Periprocedural complications

Major complications at day-three follow-up are shown in Table 30 and described below.

Vascular complication (VC)

Including perforations, cardiac tamponade and bleeding, VC was the most commonly reported periprocedural complication reported in 23 studies that collectively enrolled 4,646 patients. The rate of VC was significantly higher in the TF (n = 2,580) than in the TA group (n = 2,066), (13.1% vs 6.6%; p < 0.01). Similarly, the rate of major bleeding reported in 12 studies that comprised 3,053 patients was significantly higher in the TF (n = 1,544) than the TA group (n = 1,509) (6.6% vs 4.1%; p < 0.01). These results show a similar trend as in Leon et al. who indicated that the larger size of catheters used for TF procedures led to a high incidence of vascular complications and bleeding.³⁰

Neurologic events (major or minor strokes and transient ischemic attack)

Stroke (major or minor)

Fifteen studies reported this complication which occurred more significantly in the TF group (n = 1,657) than the TA group (n = 625), (1.9% vs 0.7%; p = 0.02). Nuis et al.¹¹⁸ suggested that further investigation is required to demonstrate whether embolic protection devices during the procedure could reduce the incidence of stroke.¹¹⁸ Overall, there was no indication of minor stroke or transient ischemic attack among studies that reported these events during the periprocedural follow-up.

Renal replacement therapy (RRT)

The rate of RRT for acute kidney injury in the two studies of the TF group (n= 60) and in the three studies of the TA group (n = 81) was 1.7% and 2.5%, respectively.

Arrhythmia

The rate of arrhythmia in the two studies (n = 172) that reported this complication in the TF group was 6.7% compared to 9.0% in a single study of the TA group (n = 177).

Myocardial infarction (MI)

The pooled average for MI representing 14 studies was significantly higher in the TA group (n = 921) than the TF group (n = 1,958), (1.7% vs 0.5%; p = 0.01).

3.7.2 Complications at 30 days

Complications at 30 days post-TAVI across all clinical studies are summarized in Table 31 and discussed below.

Major vascular complications (VC)

Vascular complications were not uniformly defined among studies. For instance, some studies included dissection, perforation or cardiac tamponade as a vascular complication whereas others included bleeding as an access site complication. Only seven studies used the standardized VARC definitions for vascular complications. Thus, based on the advice of the methodologists on the supervisory committee, these different definitions of vascular complications were collapsed into homogeneous categories (Appendix C, Table 8).

Seven studies did not report rates of vascular complications. The pooled average for VC based on reports from the remaining 26 studies comprised 5,945 patients. The rate of vascular complications occurred more significantly in the TF group (n = 3,813) than the TA group (n = 2,132), (10.2% vs 5.0%; p < 0.01). Conversely, the patients in the TF group (n = 1,232),^{116,120,121,123,141-143} who exclusively received the SAPIEN valve with a large sheath size (22 – 24 French; 7.3 – 8 mm in diameter), had a significantly higher rate of vascular complications than the patients in the TF group (n = 709),^{118,125-127,137} who only received the third generation CoreValve device (18 French sheath; 6 mm in diameter) (7.2% vs. 4.0%; p < 0.01). This finding suggests that the use of smaller sheaths and catheters could reduce the incidence of vascular complications.¹²³

A similar trend was apparent in the comparative studies where a higher incidence of VC was associated with the TF intervention (Table 32). For instance, in the RCT that enrolled inoperable patients and where 83.3% of patients underwent BAV, the rate of VC was significantly higher than in the MM group. Of note, a BAV access may require a 10 to 13 French sheath⁷¹ (3.3 – 3.7 mm) instead of the 22 or 24 French sheath used in the inoperable RCT.³⁰ In Smith et al.,¹¹⁶ the rate of VC of the TF intervention was significantly higher than in the SAVR arm. Similarly, when compared to the TA intervention, the incidence of VC was significantly higher than that of the TA intervention (14% vs 3.8; p < 0.01). In Johansson et al. the authors attributed the significant difference in VC between TF and TA approaches to large sheaths (30% vs 0%; p = 0.01).¹²⁰ However, more rigorous assessments are needed to justify this observation. Edwards Lifesciences is currently

performing an open-label RCT comparing the smaller SAPIEN XT valve (18 French) to the SAPIEN valve.¹⁵⁹

Major/life threatening bleeding

Since bleeding was related to vascular complications, it is likely that the same patient could have experienced both complications.^{30,126} The incidence of major/life threatening bleeding after TAVI was reported in 21 studies that enrolled 4,325 patients. The rate of this complication was significantly higher in the TF (n = 2,741) than the TA group (n = 1,233), (13.7% vs 5.8%; p < 0.01).

In the comparative studies, Leon et al.³⁰ attributed the large access sheaths, in the TF group, to the occurrence of VC and bleeding events as compared to the MM group (including BAV) (see Table 33).

Neurological events at 30-days

Few of the studies differentiated between major and minor stroke. Except for studies that explicitly reported stroke as “major” or “minor,” those which reported this event only as “stroke” were categorized as major; only seven studies reported the rate of TIA^{30,116,122,127,135,143,144} (see Table 31). In addition, studies that did not report a definition for stroke presented a different outcome. For instance, for the TF group Danenberg et al.,¹⁴⁴ Avanzas et al.¹³⁷ and Nielsen et al.¹⁴⁹ reported a 0% rate of stroke at 30-days as well as Zierer et al. for the TA group¹¹⁹ (Table 31).

Stroke (major or minor)

Stroke is an important complication after TAVI. Thirty studies, comprising 7,346 patients, reported this complication. A significantly higher rate of stroke occurred in the TF group (n = 3,909) in comparison to the TA group (n = 3,437), (3.9% vs 1.7 %; p < 0.001).

In the comparative studies (Table 34), Leon et al., who reported a significant incidence of stroke in the TF group as compared to MM (p = 0.03), concluded that the use of smaller sheaths and cerebral protection devices may reduce the incidence of neurological events, including TIA and stroke.³⁰ In the high risk patient RCT, the incidence of stroke was higher in the TF than in the surgical group, but not statistically significant. However, when combining all neurological events, the difference was

significantly higher in the TF than the SAVR groups (5% vs 1.7%; $p = 0.04$).^v In the TA group, the rate of all neurological events tended to be higher in the TA than the SAVR with zero occurrence of TIA reported (6.8% vs 4.2%; $p = 0.43$).^{vi}

Transient ischemic attack (TIA)

A transient ischemic attack is defined as a reversible neurological event that lasts less than 24 hours. Overall, only seven studies reported this event with a non-significant higher incidence in the TF group compared to the TA group (0.6% vs 0.0%; $p = 0.6$).

Acute kidney injury (AKI) Stage 3 / renal replacement therapy (RRT)

Acute kidney injury was an important complication associated with TAVI, particularly when requiring post-procedural RRT. Of the 17 studies that enrolled 2,124 patients (1,680 TF and 444 TA), the AKI rate was higher in the TA group than in the TF group (4.1% vs 2.8%; $p = 0.17$), but not statistically significant. In contrast, in the 20 studies that reported RRT, the rate of this complication was significantly higher in the TA than the TF group (7.3% vs 2.5%; $p < 0.001$).

Thomas et al.^{121,140} ($n = 463$ TF / $n = 575$ TA) reported that preprocedural renal dysfunction, which was significantly higher in the TA than the TF group (32.9% versus 26.3%; $p < 0.024$),^{vi} was associated with a higher rate of RRT at 30 days in the TA group in comparison to the TF group (7.1% vs 1.3%; $p < 0.0001$). After assessing preprocedural AKI and one year mortality, the authors identified a significantly higher association between mortality due to renal failure in the TA group.¹²¹

Sinning et al.¹³⁶ ($n = 77$) reported that the incidence of AKI was significantly related to peripheral arterial disease in patients with AKI at baseline ($n = 20/13$) compared to patients with no AKI ($n = 57/22$), (65% vs 39%; $p = 0.04$). In Smith et al.,¹¹⁶ unlike in the other studies, in preprocedural patient screening excluded those with renal insufficiency creatinine > 3.0 mg/dL (i.e., AKI stage two and higher) and their results at 30 days, did not show a statistically significant difference between the TA and TF groups in those patients requiring RRT (3.9% vs 2.5%; $p = 0.5$). Overall, these findings indicate that a history of preprocedural renal insufficiency could be a predictor of RRT after TAVI.

^v P value obtained from Smith et al., 2011, Supplementary Appendix¹¹⁶

^{vi} P value obtained from Smith et al. 2010

In the comparative studies, no significant differences occurred in the rate of RRT between TAVI and control groups at 30 days, including TF compared to TA in Smith et al.¹¹⁶ and Johansson et al.,¹²⁰ (3.7% vs 7.0%; $p = 0.21$) and (20% vs 3.3%; $p = 0.15$), respectively (Table 35).

Arrhythmia (bradycardia, tachyarrhythmia and atrial fibrillation)

Seven studies that collectively enrolled 1,575 patients (1,420 TF and 155 TA) reported this complication rate with a significantly higher occurrence in the TA group than in the TF group (9.7% versus 2.5%; $p < 0.001$). According to Smith et al.,¹¹⁶ patients who undergo SAVR are more likely to be associated with new onset atrial fibrillation, because the incidence is higher. This was demonstrated with the TF approach compared to the surgical arm (Table 36). As the TA approach requires a minor surgery, (a left mini-thoracotomy) this could result in a higher onset of arrhythmia than the TF approach. The same trial reported a higher rate of arrhythmia in the TA group (11.5% vs 7.4%; $p = 0.20$), but the difference did not reach statistical significance. Johansson et al.¹²⁰ reported three cases in the TA versus none in the TF group ($p = 0.56$).

Although it is not an independent risk factor associated with mortality, arrhythmia may increase hospital costs due to the longer hospital stay required.¹⁶⁰

Myocardial infarction (MI)

The rates of MI were relatively low: 19 studies reported this complication comprising 3,083 patients in the TF and 964 patients in the TA group. The pooled average tended to be similar between both groups (1.8% vs 1.6%; $p = 0.7$). Yong et al. noted that the depth of prosthesis insertion and the presence of peripheral artery disease could play a role in the occurrence of MI, which would also result in longer procedural times (in minutes: 93 ± 30 vs 77 ± 21 ; $p < 0.01$).¹³¹ There was no significant difference between TAVI and controls across the comparative studies (Table 37).

Permanent pacemaker implantation (PPM)

Reported in 28 studies that enrolled 6,255 patients (3,276 TF and 2,979 TA), the need to implant a permanent pacemaker was the most commonly reported complication. The rate of PPM was significantly higher in the TF than in the TA group (20% vs 7.3%; $p <$

0.01). This substantial difference between the two groups led to further data analysis to identify whether a possible third variable (e.g., the type of valve used) would reveal different results.

After finding two studies that reported a substantially higher PPM rate in the Medtronic CoreValve group than in the Sapien-Edwards group, Moat et al.⁴⁶ 24.4% (110/451) vs 7.4% (30/408); $p < 0.001$ ^{vii} and Zahn et al.,¹³⁵ 42.5% (240/565) vs 22% (22/100); $p < 0.01$, two subgroups were formed from the original TF group to separate Edwards SAPIEN studies from the CoreValve studies with regard to PPM events. Results revealed a new rate three times higher for patients ($n = 1,989$) who received the CoreValve compared to patients ($n = 2,867$) who received the SAPIEN valve in the TF group (26.5% vs 8.2%; $p < 0.01$).

In contrast, there was no significant difference in the number of PPMs between the pooled total of TF ($n = 2,867$) and TA groups ($n = 2,979$) with the Edwards SAPIEN valve (8.2% vs 7.3%; $p = 0.21$). These findings suggest that the use of CoreValve prostheses could significantly increase the rate of PPM in relation to Edwards SAPIEN valve.

No comparative study reported a significant difference between TAVI and their respective controls (**Table 38**).

Endocarditis

Reports on endocarditis at 30 days were rare, with just five incidents in the seven studies reporting this complication (Table 39). In the TA group, Unbenhaun et al.¹⁴⁶ and Walther et al.¹⁴⁵ reported two and one incidents of endocarditis, respectively. In the comparative studies, the SAVR groups of Smith et al.¹¹⁶ and Zierer et al.,¹¹⁹ each reported one incident of endocarditis. No endocarditis was reported in the TF group.

Overall, at 30 days, several studies discussed the relationship between complications, patient baseline characteristics, and clinical experience.^{123,129,134,140}

^{vii} P value obtained from Moat et al.¹³⁴ and Zahn et al.¹³⁵

3.7.3 Complications at one year

The six studies that reported clinical complications at one-year follow-up are illustrated in Table 40. As Gilard et al.¹²⁹ (n = 2,928) did not report complications at 30-day follow-up, the present analysis could not compare complication rates (e.g., AKI, PPM) between 30-days and one-year post-TAVI.

Major vascular complications (VC)

The rate of VC was reported in three studies that enrolled 3,455 patients (2,784TF and 671TA). The pooled average showed that VC occurred more significantly in the TF than the TA group (4.7% vs 2.2%; p < 0.01).

In the comparative studies, Table 41 shows a similar trend in findings reported by both trials with the TF approach compared to MM and SAVR arms, as opposed to the TA compared to the SAVR arm. The occurrence of VC in Smith et al.,¹¹⁶ was also significantly higher in the TF than the TA group, (14.4% vs 3.8%; p < 0.01).

Table 42 shows that new events of major VC from 30 days to one year were rare and did not differ significantly between the groups. This indicates that vascular complications were procedure-related.

Major or life threatening bleeding

The pooled average in four studies comprising 3,636 patients (2,965 TF and 671 TA) showed that the incidence of major or life threatening bleeding after TAVI did not differ between these two groups at one-year follow-up (6.1% vs 5.8%; p = 0.75). Ussia et al. reported only two incidents of major bleeding within this time interval.¹²⁶

In Smith et al.,¹¹⁶ there was no statistically significant difference in the rates of bleeding between the TF and the TA groups at one year or from 30 days to one-year follow-up: (16.2% vs 11%; p = 0.3) and (6.7% vs 2.3%, p = 0.1), respectively (Table 43 and Table 44). In contrast, Table 44 shows that the rate of new bleeding events in the SAVR arm was significantly higher than the TA approach (p < 0.01).

Neurological events at one year

Major and minor stroke

Table 40 shows the four studies comprising 3,636 patients (2,965 TF and 671 TA) that reported major and minor stroke at one-year. The pooled average showed no significant difference between the TF group and the TA group (4.1% vs 5.2%; $p = 0.2$).

In the comparative studies (Table 45) Smith et al.¹¹⁶ reported similar findings for both TAVI groups compared to SAVR, and no significant difference between the TF and TA groups (4.6% vs 8.6%; $p = 0.10$). However, Leon et al.³⁰ found a significantly higher rate of stroke in the TF group than in the MM group.

For non-cumulative events, Table 46 shows that most strokes occurred during the first 30 days, with no significant difference between TAVI and control groups. This trend was also reported in the high-risk patient RCT between TF and TA groups (0.8% vs 1.9%; $p = 0.58$).

Transient Ischemic Attack (TIA)

The occurrence of this neurologic event at one-year was only reported in the two RCTs.^{30,116} There were no significant differences between the TAVI and control groups, including TF and TA groups (1.8% vs 3.7%; $p = 0.43$) (Table 47). Similarly, rates of all neurological events (i.e., all strokes and TIA) were higher in the TF (6.4% vs 2.8%; $p = 0.07$)^{viii} and TA groups (13% vs 8.0%; $p = 0.28$) than in the SAVR group, but unlike at 30-days, this was not statistically significant. Table 48 shows that new events of TIA between 30 days and one year were uncommon in both the TF and the TA groups (0.5% vs 3.7%; $p = NS$).

Acute kidney injury (AKI) /renal replacement therapy (RRT)

Table 49 shows that RRT was only reported by both RCTs at 1-year, no statistically significant difference between TAVI and control groups was found. This was also observed in Smith et al., where the TF group was compared to the TA group (5.1% vs 5.8%; $p = 0.74$).¹¹⁶ Table 50 shows that new events of RRT across the RCTs were rare,

^{viii} P value obtained from Smith et al., 2011, Supplementary Appendix

with no significant difference among TAVI and control groups. The same trend was seen with the TF compared to the TA groups (2.5% vs 1.9%; 0.68).

Arrhythmia (bradycardia, tachyarrhythmia and atrial fibrillation)

This complication was reported only in the RCTs at one-year follow-up and was less frequent in the TAVI than in the control groups (Table 51). The cumulative rate of arrhythmia in the SAVR group was higher than in the TF group and approached statistical significance ($p = 0.05$). However, Table 52 shows that new events of arrhythmia were significantly higher in the TF group compared to SAVR. Conversely, between the two approaches, the TA group showed a higher incidence (14.4% vs 11.1%; $p = 0.34$), but it was not statistically significant.

As previously reported at 30-day follow-up, no significant new onset cardiac- arrhythmia occurred in the SAVR group between day 30 and year one. In fact, new onsets of arrhythmia occurred more frequently in the TF group, with no explanations provided in the analysis as a possible way to justify this shift. In contrast, the rates did not differ between the TF and the TA groups (3.7% vs 2.9%; $p = 1.0$) (Table 52).

Myocardial infarction (MI)

The incidence of MI was relatively low, while the pooled average was higher in the TA ($n = 671$) than the TF group ($n = 2784$) (1.5% vs 0.75%; $p = 0.17$), the difference was not statistically significant. The largest Registry study, Gilard et al.,¹²⁹ showed a higher rate of MI in the TA group than in the TF group (1.8% vs 0.8%; $p = 0.05$), with no statistically significance difference. The authors did not provide an explanation for the occurrence of such a complication.

In the comparative studies, the rates of MI was also low and there was no statistically significant difference between TAVI and their respective controls either at one year or new onsets between 30 days and one-year follow-up (Table 53 and Table 54).

Permanent pacemaker (PPM)

Three studies that enrolled a collective total of 3,455 patients reported PPM outcomes at one-year follow-up. The overall pooled rates of PPMs were higher in the TF group ($n =$

2,784) than in the TA group (n = 671): 13.5% vs 12.4%; p = 0.33, but were not statistically significant.

In the comparative studies, Table 55 and Table 56 show the same trend for the TAVI interventions compared to their respective controls at one year and for new events of PPM between 30 days and one year. This includes the TF vs TA groups of Smith et al.,¹¹⁶ (5.5% vs 6.1%; p = NS) at one year and (2.8% vs 2.2%; p = NS) from 30 days to one-year.

Unlike both RCTs, which used only the Edwards Sapien valve, Gilard et al.¹²⁹ reported a rate of PPMs significantly higher with patients who received a Medtronic CoreValve (252/1043) compared with those who received an Edwards Sapien valve (243/2107): 24.2% vs 11.5%; p < 0.001.

Endocarditis

Table 57 shows that the occurrence of endocarditis was rare at one year, accounting for four onsets in both RCTs compared to three onsets in the control groups. Table 58 indicates that all of these onsets occurred between 30 days and one year. Zierer et al. reported only one event in the SAVR group compared to the TA approach.¹¹⁹

There were no reports of valve deterioration in the first year.

3.7.4 Complications at two years

Table 59 summarizes clinical complications reported by both RCTs and one case series at two-year follow up based on raw data. Stroke and endocarditis were the only complications reported across the three studies at this time interval. Buellesfeld et al.¹²² outlined that the risk of major complications at two years was associated with pre-existing comorbidities before the intervention.

Major Vascular complications

Table 60 shows that in the high-risk patient RCT, the TF group demonstrated a significant difference in major VCs as compared to SAVR. The same trend was observed between the TF and the TA groups (15% vs 3.8%; p < 0.01). This is in contrast to the TA

group when compared to SAVR. However, there was no significant difference in the number of new events from one to two-year follow-up between TAVI (including TF and TA) and SAVR (Table 61).

Major Bleeding

Although a significant difference was observed between TAVI and controls (Table 62) at two years, including TF compared to TA (21.5% vs 12.4; $p = 0.04$), new events between one and two years were uncommon (Table 63).

Neurological events

Stroke (major or minor)

Across 495 patients, the pooled average for stroke was significantly higher in the TF than the SAVR group (9.7% vs 4.9%; $p < 0.001$). In the comparative studies, only the RCT with inoperable patients showed a significant difference between TAVI and MM (Table 64). However, new events of stroke between TAVI and controls from one to two years were uncommon (Table 65). The same trend was seen between TF and TA groups (1.1% vs 2.9%; $p = 0.4$).

Though the rate of stroke was higher in the TF group than the MM at two years (13.8% vs 5.5%), there was no significant difference in the number of new stroke events between years one and two (Table 65). Similarly, new events of complications such as VC (Table 60), major bleeding (Table 62), RRT,(Table 66) MI (Table 68), PPM(Table 69) and endocarditis (Table 71) were rare, with no statistical significance when compared to MM and SAVR.

Overall, there was no report of valve deterioration at two year follow-up.

3.7.5 Complications at three years

Ussia et al.¹²⁶ reported that major bleeding remained the most prevalent complication followed by major stroke and myocardial infarction (Table 74). None of the studies throughout all specific time intervals described above observed any evidence of structural valve deterioration or other valve dysfunction.

3.8 Assessment of survival

Twenty three studies reported survival at one-year follow-up, including seven comparative studies. All but three of these studies^{30,119,136} reported the use of Kaplan-Meier survival estimates, which is a statistical method used to estimate observations that are censored (missing) at a specific time point.¹⁶¹

3.8.1 Survival at one year

In the comparative studies, one-year survival ranged from 69% to 77.8% in the TF group and 67% to 76% in the TA group. Leon et al.³⁰ reported 69.3% rate compared to 49.7% in the MM arm. Yet the survival rate of the SAVR arms was higher than that of the TA among the comparative studies (Table 75).^{116,119,120}

In the case series, the probability of surviving at one year ranged from 72.6% to 88% in the TF group and 67.7% to 82.7% in the TA group (Table 76).

3.8.2 Survival at two years

In the comparative studies (Table 75), the survival rate in the TF group was higher in Smith et al. (69.1%)¹¹⁶ than in Leon et al. (57%).³⁰ The two-year survival estimates in the case series studies for the TF and TA approaches ranged from 52% to 80% and from 60% to 71.5% respectively (Table 76).

3.8.3 Survival at three years

The three-year survival estimate was 58% in two TA studies^{124,145} and 52% - 65% in two TF studies (Table 76).^{126,127}

3.9 Rehospitalisation after TAVI

The data on rehospitalisation was limited (Table 77), with only seven studies reporting this event, including both RCTs and their two-year follow-up studies. Except for the high risk surgical trial, no other study reported data on hospital readmission specifically on

the TA implantation. Hammerer et al.¹²⁸ indicated a lack of data on rehospitalisation after TAVI.¹²⁸

Rehospitalisation due to cardiac reasons in PARTNER B was 22.3% after TAVI compared to 44.1% in the control group. At two-year follow-up,^{ix} the probability of experiencing a recurrent hospitalisation in the TAVI group compared to the MM arm was 35% versus 72.5%. In the high risk operable RCT, both at 30 days and at one year, rates were similar in both groups, with the risk of readmission to hospital occurring in approximately 58 patients (18.2%) in the TAVI group and in 45 patients (15.5%)¹ in the SAVR group (p = NS).^x This trend was observed at two-year follow-up, when the probability of hospital readmission after TAVI (TF and TA) compared to SAVR was not statistically significant.

The three-year risk of hospital readmission was 34.4% reported by a single case series study based on the TF approach.¹²⁶ Based on the current findings, the lack of hospital cardiac readmission data creates a challenge to determining the effectiveness and economic impact of TAVI.¹⁶²

3.10 Assessment of efficacy

A summary of the reported echocardiographic findings and post-TAVI outcomes at one-month, one-year, two-year and three-year follow-up is provided in Table 78. Seventeen studies presented preprocedural echocardiographic outcome measures that indicated severe AS.²⁴ Overall, 23 studies reported at least one postprocedural outcome. Several studies reported findings without distinguishing which TAVI approach was used; and no studies suggested that one approach was superior to the other in terms of echocardiographic outcomes. Ewe et al.¹⁴¹ concluded that the two approaches were comparable in this respect.

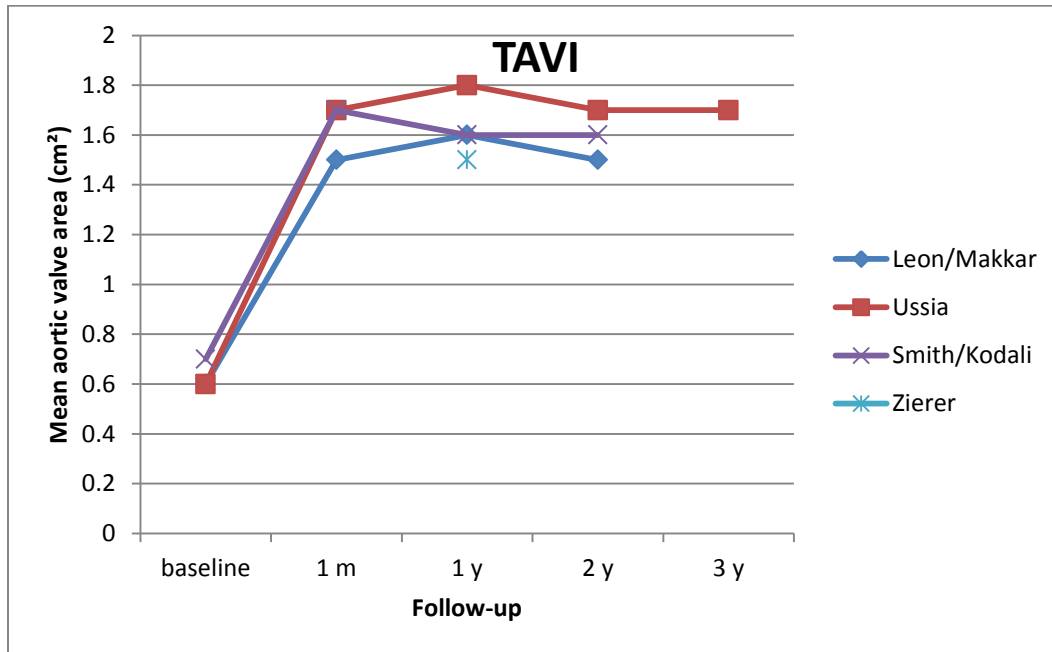
^{ix} Based on Kaplan-Meier estimates at the specific time point

^x P-value reported by the authors

3.10.1 Mean aortic valve area (AVA)

The AVA for both pre-procedural baseline and one-month follow-up was based on a subset of eight studies that enrolled a total of 1,123 patients.^{xi, 124,126,128,139,141-143,149} The pooled mean AVA improved significantly from $0.63\text{cm}^2 \pm 0.2$ to $1.6\text{cm}^2 \pm 0.4$; $p < 0.001$ after TAVI. Ye et al.¹²⁴ reported that the AVA remained stable at two-year follow-up ($1.6 \pm 0.3 \text{ cm}^2$). Of the studies with follow-up beyond 30 days, only Ussia et al. reported this outcome, showing a slight increase to a mean of $1.8 \text{ cm}^2 \pm 0.4$ at one year followed by a slight decrease to a mean of 1.7 cm^2 at two and three-year follow-up. Figure 6 also includes results from studies that did not assess their entire patient population at baseline or provide 30-day outcomes, yet reported longer term follow-up.

Figure 6. Assessment of aortic valve area (AVA)



Two studies (not included in the pooling) provided data on AVA compared to SAVR at one year. While the first, the high risk patient RCT,^{116,117} demonstrated improvement on the mean AVA based on as-treated data ($1.59 \pm 0.48 \text{ cm}^2$ versus $1.44 \pm 0.47 \text{ cm}^2$; $p = 0.002$)

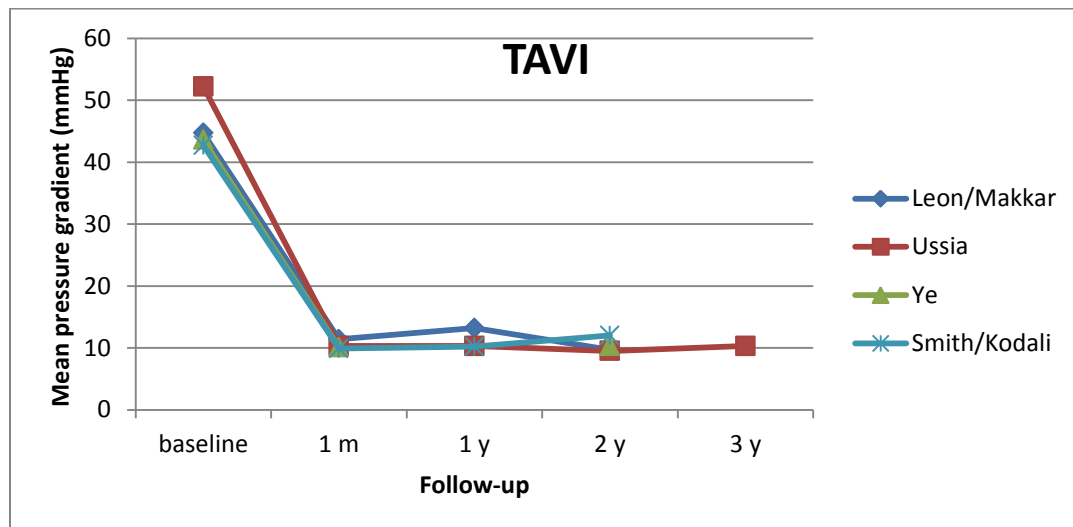
^{xi} Only studies that started the analysis with all patients at baseline were considered

the other study, Zierer et al.,¹¹⁹ based on intention-to-treat (ITT) data, showed a slightly inferior difference compared to SAVR ($1.5 \pm 0.8 \text{ cm}^2$ vs $1.7 \pm 0.5 \text{ cm}^2$; $p = 0.3$).

3.10.2 Mean pressure gradient

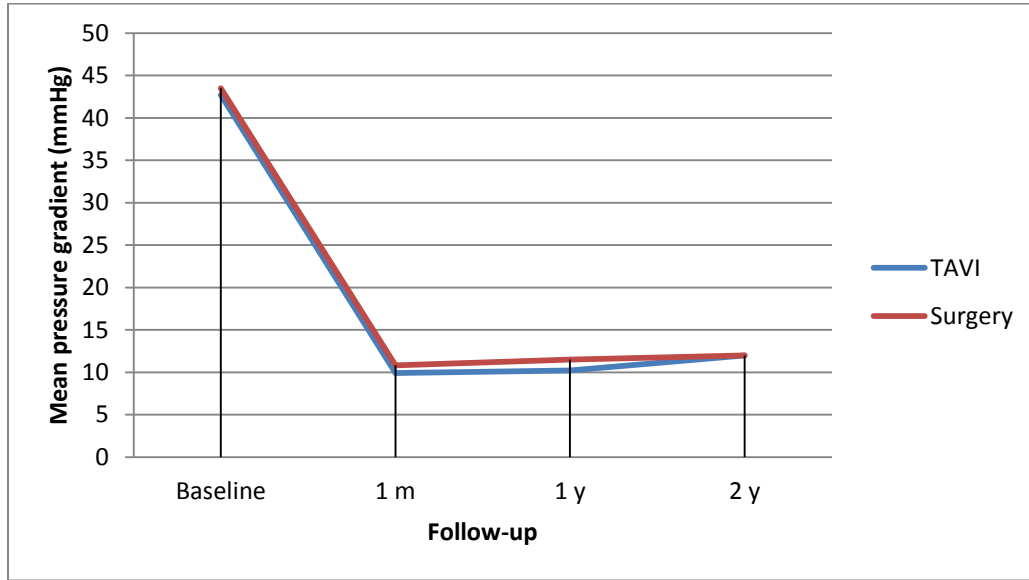
The assessment of the transaortic mean gradient for pre-procedural baseline and one-month follow-up was based on a subset of 10 studies, with 1,143 patients.^{124,126-128,139,141-144,148} The pre-TAVI mean pooled gradient was $49.9 \pm 16.1 \text{ mmHg}$ for all patients. At 30 days, regardless of the TAVI approach used, the pooled mean gradient fell significantly to $10 \pm 4.2 \text{ mmHg}$. Ussia et al.¹²⁶ reported this event showing a stable result at a mean of $10.3 \pm 3.1 \text{ mmHg}$ at 1-year; these values remained stable at three-year follow-up with a mean of $10.3 \pm 4.7 \text{ mmHg}$. In addition, Ye et al.¹²⁴ reported that the mean gradient remained stable at two years ($10.3 \pm 5.9 \text{ mmHg}$). Figure 7 also includes some studies that did not assess all patients at baseline and those that provided longer term follow-up.

Figure 7. Mean pressure gradient



The values reported in the surgical RCT at one-year follow-up show a slight decrease for TAVI compared to the surgical arm at one year but remain stable at two-year follow-up (see graph below).

Figure 8. Mean pressure gradient Smith & Kodali RCT



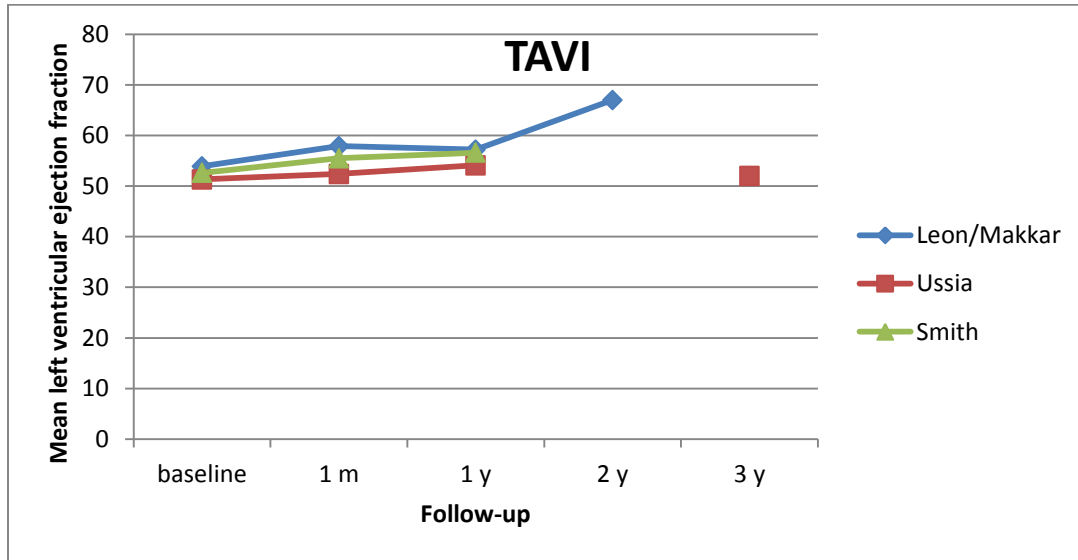
Zierer et al.,¹¹⁹ reported a significant improvement with SAVR compared to TA patients at one year (7.3 ± 3.7 vs 9.6 ± 3.7 ; $p = 0.02$).

3.10.3 Left ventricular ejection fraction (LVEF)

A sub-set of six studies that enrolled a collective total of 881 patients, reported the pre-procedural baseline and the effect of TAVI on the LVEF at 30-day follow-up.^{126,127,139,141,145,148} The pre-TAVI pooled mean was $53.4\% \pm 14\%$. At 30 days and regardless of the TAVI approach, the pooled mean increased to $56\% \pm 13.3\%$. However, the difference was not significant ($p = \text{NS}$).

Figure 9 shows four studies that reported 30-day and long-term follow-up.^{31,116,126,163} Of these, Ussia et al.¹²⁶ reported an improvement of $54\% \pm 10\%$ at one year and a slight decrease to $51.8\% \pm 13.9\%$ at three-year follow-up. Another study, Ye et al.,¹²⁴ (not included in the figure) reported only two time intervals and found an improvement from 55.5 ± 13.5 at baseline to 61.2 ± 7.0 at two-year follow-up.

Figure 9. Comparison of studies reporting mean left ventricular ejection fraction



3.10.4 Paravalvular aortic valve regurgitation (AR): moderate/severe

A subset of 15 studies that involved approximately 3,170 patients (2,550 TF and 620 TA) reported data on moderate/severe paravalvular AR at one month.^{119,124-}

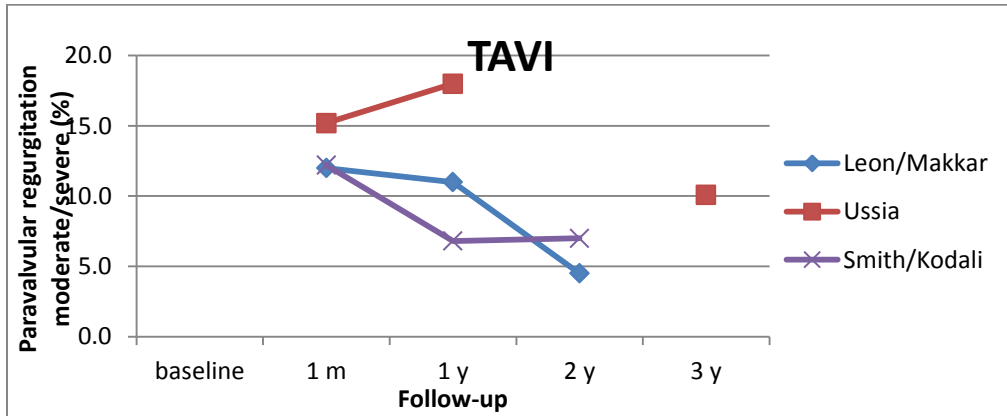
^{128,131,134,135,137,140,142,145,147,148} The overall rate for this complication was 7.2% and higher with the TF approach (7.4% vs 5.7%; $p = 0.1$), but the difference was not statistically significant. Of these studies, Ussia et al.¹²⁶ reported an increase in the rate of AR at one year, followed by a steep decline at three-year follow-up.

However, the authors recommend caution when interpreting these results, as these data are based on 129 and 89 patients at one and three-years follow-up.¹²⁶

It is important to note that one large Registry study, Moat et al.,¹³⁴ reported a significantly higher rate of moderate to severe AR with the Medtronic valve compared with the Edwards SAPIEN valve (76/439 (17.3) vs 39/405 (9.6); $p = 0.001$).^a

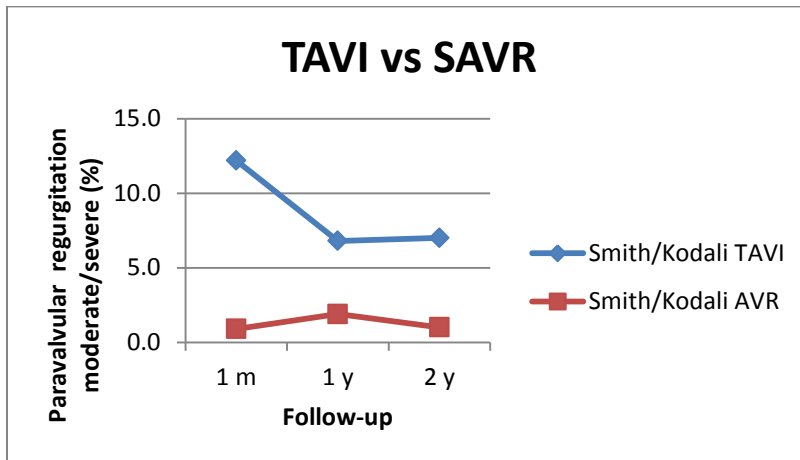
^a P-value obtained from Moat et al. 2011

Figure 10. Paravalvular regurgitation in TAVI studies



Overall, the study results for paravalvular regurgitation at longer term follow-up were quite disparate. For instance, while the medically managed trial reported a significant decrease in AR at two years, the surgical trial reported a slight increase during the same period. Some studies reported that AR was present to some degree in most patients throughout follow-up.^{123,124,142} According to Ye et al., correct positioning of the valve and measurement of the aortic annular size are associated with clinical experience and will lead to a more appropriate selection of valve size.¹²⁴

Figure 11. Paravalvular regurgitation – TAVI vs SAVR



Moderate/severe paravalvular regurgitation was more frequent after TAVI than surgical aortic valve replacement ($p < 0.001$).^{xii} This was associated with late mortality.¹¹⁷

3.10.5 Overall echocardiographic observations

In respect to short-term efficacy, post-TAVI improvements of echocardiographic measurements seem encouraging, regardless of the access route, including the mean calculated AVA, the transaortic mean gradient and LVEF. The overall rate of aortic regurgitation which is an independent predictor of mortality (moderate/severe) was present in 7.2% of patients.^{127,134} In terms of long term follow-up, except in Ye et al.¹²⁴ (n = 71), which indicated improvements with the AVA, aortic-valve gradient and LVEF, all of the other studies reported incomplete outcome data with a considerable loss of follow-up. Both RCT's reported data based on as-treated analyses with a considerable loss of follow-up across their studies.⁹⁷

Overall, long-term outcomes were scarce, making it impossible to properly evaluate the durability of the valve. Therefore, the results should be interpreted with caution.¹²⁶

Functional improvement per New York Heart Association (NYHA)

The NYHA reports information on the clinical status of TAVI based on the following functional scale distribution:

- Class I – No limitation of daily physical activity
- Class II – Ordinary physical activity results in fatigue and palpitation
- Class III – Less than ordinary physical activity leads to fatigue and palpitation
- Class IV – Unable to carry out any physical activity with cardiac symptoms at rest

Fourteen studies reported the distribution of patients per NYHA class at least in some degree (i.e., a single functional scale distribution) before and after TAVI (Table 79).

Three of these studies (n = 627)^{30,116,164} provided ITT (except for 30-day follow-up in one

^{xii} Data provided by the author

trial)^{xiii} data analysis for TAVI and reported NYHA class^{xiv} per functional class at baseline, 8.4%, 48.1% and 43.5% were in NYHA class I and II (combined), class III and class IV respectively. At one-month follow-up, 74%, 21% and 4% were in classes I and II, III and class IV respectively. The improvement of functional status was sustained, with follow-up reported by both RCTs (n = 527) at one year: 81.5%, 15.9% and 2.6% and at two year with 83.9%, 14.8% and 1.6% in classes I and II, III and class IV, respectively.

In the surgical trial,^{116,117} the differences in functional class between TAVI and SAVR groups did not reach statistical significance regardless of the follow-up interval. This was unlike the medically managed trial, where the differences in functional class between both groups were statistically significant at all follow-up intervals.^{30,31} One case series reported functional improvement at three years: 55%, 10%, 0% were in NYHA class I/II, III and IV respectively.

A few studies described a reduction of at least one functional class in most patients, notably where patients were more likely to be in class I or II at baseline, compared to class III or IV at 30 days^{127,149,143} or one year.^{124,141}

None of the studies above reported findings with regard to surviving patients in functional class IV at any follow-up interval.

3.11 Health related quality of life (HRQoL)

Fourteen studies reported data on HRQoL outcomes comparing patients with severe symptomatic AS before and after TAVI (TF and/or TA)^{xv} from one to 12 months (see Table 80). Two studies by Reynolds et al. (2011 and 2012) assessed TAVI patients from both RCTs.^{165,166} In addition, two studies by Ussia et al.^{167,168} reported that the HRQoL of TAVI patients five months after TF TAVI implantation was comparable to that of the general Italian population over the age of 75 years (n = 5,283).¹¹²

Across all studies, the mean STS surgical risk score at baseline varied, ranging from 7.9 to 18.1. This suggests patient baseline characteristics differed. Thus, comparison among

^{xiii} Mortality excluded in the 30-day analysis (5%)

^{xiv} This thesis combined classes I and II for the analysis

^{xv} Few studies reported using the subclavian approach (ranging from three to five per study)

studies should be made with caution. Seven studies used both STS and EuroSCORE risk scores.^{166,169-173}

Overall, findings show significant improvement compared to baseline at one-year follow-up. It appears that the ultimate value of TAVI will depend on careful selection of patients who do not have extreme comorbidities that may overshadow the benefits of TAVI.

Several different quality of life measures were used in the included studies:

1. The Short Form 36 (SF-36) questionnaire, a validated measure used to assess the overall physical and mental status.
2. The Short Form 12 (SF-12 and SF-12v2^{xvi}) health survey, a simplified and shorter version of SF-36.
3. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ). Both questionnaires are used to quantify specific concerns of heart failure patients.
4. The EuroQoL instrument (EQ-5D) which complements other forms of quality of life measures by assessing the seriousness of conditions.¹⁷⁴

Higher questionnaire score results after TAVI for the SF-12, SF-12v2, SF-36, KCCQ and EQ-5D questionnaires indicate an improvement in quality of life for the patient. An exception is the MLHFQ score where a lower score result after TAVI represents a higher quality of life improvement for the patient.

All 14 studies reported a statistically significant improvement after TAVI based on at least one quality of life measure (Table 81). The four studies that used the SF-36 demonstrated improvement in the physical component summary (PCS) in different follow-up intervals (i.e. three, six and 12-month follow-up).^{169,175-177} The SF-12 scores, including SF-12v2, also demonstrated a statistically significant improvement after TAVI.^{165,167,168,170,176,178} Half of these studies, using either SF-36 or SF-12, also

^{xvi} Provides 5-level responses in lieu of dichotomous response choice as in SF-12

demonstrated a statistically significant improvement in the mental component summary (MCS).^{165,167,168,176}

Two studies reported SF-36 and SF-12 (PCS and MCS) outcome scores similar to the general Italian population norms of the same age range (>75) at five and 12-month follow-up.^{167,168} Two studies presented significant improvement based on the overall MLHFQ score.^{171,179} A third study, not only marked substantial improvement in the overall MLHFQ score, but also in physical and emotional dimensions.¹⁸⁰ Two studies indicated a significant benefit of KCCQ score at 12 months.^{165,172} Of the two studies that also used the EQ-5D, one did show some improvement after TAVI which did not meet statistical significance at 12-month follow-up,¹⁷² while the other, which assessed patients from the inoperable trial,³⁰ found a significant benefit at 12-month follow-up.¹⁶⁵

Overall, these 14 studies on HRQoL, including the inoperable RCT arm,¹⁶⁵ demonstrated an important improvement in quality of life after TAVI in different time intervals up to 12 months. No information on HRQoL was available from the high risk trial.¹¹⁶

3.12 The learning curve (LC)

When assessing new surgical devices and techniques, the learning curve can have an important impact on the safety and effectiveness of the technology, and on overall outcomes.¹⁰¹

This section discusses five studies that specifically assessed the learning curve for performing TAVI for patients undergoing TF and/or TA approach (Table 82). It also includes four clinical studies that reported findings on the LC.^{123,132,146,149}

Table 82 shows that mortality was the most commonly assessed event to determine the effect of the LC.^{146,162,181,182} Gurvitch et al. observed that procedural experience was an independent predictor of 30-day mortality following TAVI.¹⁸¹ Webb et al. (n = 50 TF), who divided patients in two groups of 25 each, reported a significant difference in procedural success rate from the first to the second group (from 76% to 96%).¹⁸² In Ali et al., fluoroscopy times and radiation doses decreased significantly with the TF approach.¹⁸³ Kempfer et al. (n = 299) found a significant decrease in 30-day mortality

rates after the TA approach from 11% (n = 1 – 150) to 6% (n = 151 – 299).¹⁶² Moreover, in the same study, the one-year mortality dropped significantly, from 30.7% in the first half to 21.5% in the second half. Wendler et al. found mortality was unchanged with TA patients, and attributed this to patient comorbidities not captured at baseline.¹⁵⁵ However, there was a significant difference in aortic regurgitation and conversion to SAVR in this study (Table 82).¹⁵⁵

In the clinical studies that reported data on the LC, Webb et al.,¹²³ indicated a decrease in the mortality from the initial half to the second half of this experience, from 12.3% to 3.6%, respectively with TF patients. Nielsen et al. showed a statistically significant difference in overall mortality from 12% among the first 50 patients to 4% in the last 50.¹⁴⁹ In contrast, results from D’Onofrio et al. an Italian Registry using the TA approach, showed no significant difference between the first and second half groups.¹³² Finally, Unbehaun et al. reported a decrease in 30-day mortality rate from 6% for the first and second consecutive group of patients, to 2% for the last 100 patients.¹⁴⁶ In addition, there was a significant difference in STS score ($p = 0.001$)^{xvii} among the three groups of 100 patients each.

Other important findings were significant decrease with procedural and radiation times (see Table 82).

^{xvii} P value reported by the authors

Chapter 4. Discussion, limitations and conclusions

4.1 Discussion

During the course of this review and through discussion with the expert committee, several issues for the provision of TAVI were identified:

- the importance of comprehensive patient assessment and selection for TAVI
- the impact of the learning curve on patient outcomes and the need for specialist centres of TAVI expertise, and
- the rapid pace of changes and improvements in TAVI technology.

4.1.1 Patient selection

Most studies in this review emphasized the importance of using a multidisciplinary “Heart Team” to assess the suitability of patients for TAVI.^{75,184} Careful patient assessment and care to determine eligibility for TAVI is critical to optimize procedural short and long-term outcomes. An important role for the multidisciplinary team is in determining patient comorbidities (e.g., porcelain aorta and frailty) as current risk scores have limitations for assessing patients for TAVI.¹⁵³ Standardized patient selection criteria should provide clear and objective guidance that can be used across TAVI centres.

Patients and their families should be thoroughly informed about the treatment choices available, and the benefits and risks associated with TAVI (e.g., stroke, vascular complications, and the possible need for a pacemaker). Patient assessment should include careful consideration of their preferences and their likelihood of improved health-related quality of life for a reasonably long period of time post-TAVI.

4.1.2 Learning curve

This review identified the important role of the learning curve for TAVI. For instance, there was a significant decrease in mortality at 30 days with greater procedural experience. Moreover, the decrease in procedural and radiation times with clinical experience also contributed to improved patient safety.

4.1.3 Technological change

Given that TAVI technology is evolving rapidly, complication rates reported with earlier generations of the devices may not reflect rates with the newer devices. A study that compared the newer Edwards SAPIEN XT with the earlier Edwards Sapien valve found a significant decrease in the rate of major vascular complications, suggesting the newer devices may reduce major vascular complications.¹⁸⁵ Moreover, the latest generation of Edwards Lifesciences valves, the SAPIEN 3, with a “paravalvular sealing system,” has demonstrated promising results in the first in-human feasibility study.¹⁸⁶ Finally, the use of cerebral embolic protection devices for patients undergoing TAVI may reduce the risk of procedure-related strokes.¹⁸⁷

4.2 Limitations

This systematic review has several limitations. First, since the search was restricted to English and French publications, language bias cannot be ruled out. Furthermore, even though two independent reviewers screened all abstracts and primary studies using a standardized check list, it is possible that selection bias could have been introduced. Ideally, the second independent reviewer would have extracted data from all studies instead of 20%, to minimize reviewer errors.

Although a large number of studies were excluded to minimize the effects of patient overlap, one cannot rule out the possibility that outcomes for some TAVI patients were reported in multiple studies.

It is possible that the proposed clinical pathway presented to assist clinical experts might have biased their responses.

Accurate comparison of complication rates amongst studies was challenging due to the different definitions of complications across studies. Descriptions of patient characteristics at baseline also varied significantly, making it difficult to distinguish inoperable patients from those at high-risk.

Finally, this analysis did not have access to patient-level data; consequently it has not accounted for confounding factors that are associated with survival after TAVI.

Therefore, it is possible that the lower survival after the transapical approach may be due to the implantation technique or to existing patient comorbidities.

4.3 Conclusions

Patients with severe symptomatic AS have a poor prognosis with medical management (including BAV). Based on the studies reviewed for this assessment, the evidence demonstrates that in comparison to medical management, TAVI significantly improves survival in patients with severe symptomatic AS. TAVI appears to be a promising technology with clear benefit to this group of patients who have no further treatment options.

Based on current evidence, for patients at high risk for surgery, TAVI does not appear to significantly improve survival compared to SAVR. However, clinical outcomes (e.g. aortic regurgitation) need to be measured in comparison to SAVR. This finding is in line with a systematic review by Cao et al.¹⁸⁸

The learning curve has a significant effect on procedural success and is an independent factor for improving 30-day mortality.

The complications and risks associated with TAVI differ with the different approaches and devices used. For instance, patients who received the transapical approach have fewer vascular complications than those who received the transfemoral approach with the larger size of catheter used for this intervention. The introduction of new generations of delivery systems that use smaller catheters appears to reduce the risks of vascular complications with this approach. In addition, compared to SAVR, TAVI is associated with significantly higher rates of aortic regurgitation.

Patients who received the transapical approach had higher rates of renal failure than those who received the transfemoral approach. This is an independent risk factor for mortality and may be due to underlying patient comorbidities. Therefore, careful patient assessment is needed to minimize the risk of requiring renal replacement therapy.

Patients who received the transfemoral approach with the CoreValve device have significantly higher rates of permanent pacemaker implantation compared to those who

received the transfemoral approach with the Edwards SAPIEN valve, but the reason for this difference is not clear.

This analysis may assist physicians and decision makers in assessing the risks and benefits of TAVI for patients with severe symptomatic aortic stenosis. Patients should be fully informed of the risks, benefits and current uncertainties associated with TAVI. As the technology evolves, TAVI may diffuse rapidly, possibly with broader indications for use in an expanded patient population.

Appendices

Appendix A. Literature search strategy

1. PubMed (www.pubmed.gov; 25 Jan 2012)

Search	Query	Result
#34	Search #21 OR #32 Limits: Publication Date from 2002 to 2012	1467
#33	Search #21 OR #32	2002
#32	Search Search #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	824
#31	Search TAVI[tiab] OR TAVR[tiab] OR THV[tiab] OR PAVI[tiab] OR PAVR[tiab] OR PHVR [tiab]	543
#30	Search "partner trial"[tiab]	11
#29	Search revalve[tiab]	1
#28	Search revalving[tiab]	78
#27	Search corazon[tiab]	44
#26	Search cribier[tiab]	40
#25	Search corevalve[tiab]	250
#24	Search sapien[tiab]	192
#23	Search novaflex[tiab]	5
#22	Search ascendra[tiab]	1
#21	Search #11 AND #20	1550
#20	Search #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	347394
#19	Search Edwards[tiab]	3841
#18	Search percutaneous[ti]	39534
#17	Search "trans-apical"[ti]	19
#16	Search transapical[ti]	254
#15	Search transventricular[ti]	204
#14	Search "minimally invasive"[ti]	7065
#13	Search transcatheter*[ti]	4749
#12	Search surgical procedures, minimally invasive[mesh]	314332
#11	Search #5 AND #10	9904
#10	Search #6 OR #7 OR #8 OR #9	44467
#9	Search bioprosthesis[mesh]	7835
#8	Search heart valve prosthesis implantation[mesh]	9844
#7	Search heart valve prosthesis[mesh]	25962
#6	Search heart catheterization/methods	10096
#5	Search #1 OR #2 OR #4	16278
#4	Search (aortic[ti] OR aorta[ti]) AND valve*[ti] AND (stenosis[ti] OR implant*[ti])	2542
#2	Search aortic valve/surgery	9846
#1	Search aortic valve stenosis/surgery	6844

2. The Cochrane Library (John Wiley; Issue 1 of 12, Jan 2012)

#1	(aortic valve stenosis):ti,ab,kw or (aortic OR aorta) AND valv* AND (stenosis OR implantation):ti,ab,kw	348
#2	(heart catheterization):ti,ab,kw or (heart valve prosthesis):ti,ab,kw and (bioprosthesis):ti,ab,kw	1381
#3	(minimally invasive OR transcatheter* OR transventricular OR transapical OR trans-apical):ti,ab,kw or (percutaneous OR Edwards):ti,ab,kw	7031

#4 (#1 AND #2 AND #3)	11
(ascendra OR novaflex OR sapien OR corazon OR corevalve OR cribier OR revalving OR revalve OR	
#5 "partner trial"):ti,ab,kw or (TAVI OR tavr OR thv OR pavi OR pavr OR phvr):ti,ab,kw or (transcather	9
aortic valve implantation):ti,ab,kw	
#6 (#4 OR #5)	15
3. EMBASE (Ovid; 1980-2012 week 4)	
1 aorta valve prosthesis/ or aorta valve stenosis/	11940
2 exp aorta valve/su [Surgery]	2772
3 1 or 2	14256
4 exp heart catheterization/su [Surgery]	1
5 exp heart valve prosthesis/su [Surgery]	1
6 exp bioprosthesis/	4636
7 4 or 5 or 6	4638
8 exp minimally invasive surgery/	18936
9 transcatheter*.ti.	6385
10 minimally invasive.ti.	8664
11 transventricular.ti.	197
12 transapical.ti.	366
13 trans-apical.ti.	20
14 percutaneous.ti.	48545
15 exp Carpentier Edwards bioprosthesis/ or exp Starr Edwards valve prosthesis/	345
16 edwards.mp.	5560
17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	81799
18 7 and 17	702
19 ascendra.mp.	19
20 novaflex.mp.	21
21 sapien.mp.	620
22 corevalve.mp.	745
23 cribier.mp.	87
24 corazon.mp.	639
25 revalving.mp.	205
26 revalve.mp.	3
27 partner trial.mp.	22
28 (tavi or tavr or thv or pavi or pavr or phvr).mp.	1333
29 3 and 28	326
30 3 and 7 and 17	180
31 29 or 30	488
32 limit 31 to yr="2002 -Current"	414

4. Web of Science (Thomson Reuters; 2 Feb 2012)

7 648 #6

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Timespan=2002-2012 Lemmatization=On

6 848 #5 OR #4

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Timespan=All Years Lemmatization=On

5 474 Title=(ascendra OR novaflex OR sapien OR corevalve OR cribier OR corazon OR revalve OR "partner trial") OR Title=(tavi OR tavr OR thv OR pavi OR pavr OR phvr)

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Timespan=All Years Lemmatization=On

4 431 #3 AND #2 AND #1

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Timespan=All Years Lemmatization=On

3 62,156 Title=(transcatheter* OR "minimally invasive" OR trasnventricular OR transapical OR "trans-apical" OR percutaneous OR edwards)

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Timespan=All Years Lemmatization=On

2 7,442 Topic=("hearth catheterization" OR "heart valve" OR bioprosthesis)

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Timespan=All Years Lemmatization=On

1 21,364 Topic=("aortic valve stenosis" OR "aortic valve") OR Topic=((aortic OR aorta) AND valve AND (stenosis OR implant*))

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Timespan=All Years

5. Scopus (SciVerse/Elsevier; 10 Feb 2012)

15 (TITLE-ABS-KEY-AUTH(corevalve AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(revalv* AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH("partner trial")) OR (TITLE-ABS-KEY-AUTH((tavi OR tavr OR thv OR pavi OR pavr OR phvr) AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(transapical OR trans-apical AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH((transcatheter* OR percutaneous) AND "heart valve*" AND (aortic OR aorta))) OR ((TITLE-ABS-KEY("transcatheter aortic")) OR (TITLE-ABS-KEY-AUTH(sapien AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(cribier AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(corazon AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(ascendra AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(novaflex AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(corevalve AND (aortic OR aorta)))) AND (LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002)) 1,948

14 (TITLE-ABS-KEY-AUTH(corevalve AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(revalv* AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH("partner trial")) OR (TITLE-ABS-KEY-AUTH((tavi OR tavr OR thv OR pavi OR pavr OR phvr) AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(transapical OR trans-apical AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH((transcatheter* OR percutaneous) AND "heart valve*"

AND (aortic OR aorta))) OR ((TITLE-ABS-KEY("transcatheter aortic")) OR (TITLE-ABS-KEY-AUTH(sapien AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(cribier AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(corazon AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(ascendra AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(novaflex AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(corevalve AND (aortic OR aorta)))) 2,239

13 (TITLE-ABS-KEY("transcatheter aortic")) OR (TITLE-ABS-KEY-AUTH(sapien AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(cribier AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(corazon AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(ascendra AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(novaflex AND (aortic OR aorta))) OR (TITLE-ABS-KEY-AUTH(corevalve AND (aortic OR aorta))) 1,283

12 TITLE-ABS-KEY-AUTH((transcatheter* OR percutaneous) AND "heart valve*" AND (aortic OR aorta)) 1,497

11 TITLE-ABS-KEY-AUTH(transapical OR trans-apical AND (aortic OR aorta)) 449

10 TITLE-ABS-KEY-AUTH((tavi OR tavr OR thv OR pavi OR pavr OR phvr) AND (aortic OR aorta)) 489

9 TITLE-ABS-KEY-AUTH("partner trial") 13

8 TITLE-ABS-KEY-AUTH(revalv* AND (aortic OR aorta)) 141

7 TITLE-ABS-KEY-AUTH(corevalve AND (aortic OR aorta)) 403

6 TITLE-ABS-KEY-AUTH(novaflex AND (aortic OR aorta)) 12

5 TITLE-ABS-KEY-AUTH(ascendra AND (aortic OR aorta)) 13

4 TITLE-ABS-KEY-AUTH(corazon AND (aortic OR aorta)) 42

3 TITLE-ABS-KEY-AUTH(cribier AND (aortic OR aorta)) 149

2 TITLE-ABS-KEY-AUTH(sapien AND (aortic OR aorta)) 322

1 TITLE-ABS-KEY("transcatheter aortic") 940

6. MEDLINE (Ovid; In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (3 Apr 2012)

1	exp Aortic Valve Stenosis/su [Surgery]	6943
2	exp Aortic Valve/su [Surgery]	8844
3	((aortic or aorta) and valve* and (stenosis or implant*)).ti.	2534
4	1 or 2 or 3	15468
5	exp Heart Catheterization/mt [Methods]	10388
6	exp Heart Valve Prosthesis/	26184
7	exp Heart Valve Prosthesis Implantation/	10112
8	exp Bioprosthesis/	7928
9	5 or 6 or 7 or 8	45125

10	4 and 9	9754
11	exp Surgical Procedures, Minimally Invasive/	319229
12	transcatheter*.ti.	4742
13	minimally invasive*.ti.	7105
14	transventricular.ti.	197
15	transapical.ti.	252
16	trans-apical.ti.	19
17	percutaneous.ti.	39455
18	Edwards.ab. or Edwards.ti.	3923
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	351852
20	10 and 19	1623
21	ascendra.ab. or ascendra.ti.	1
22	novaflex.ab. or novaflex.ti.	5
23	sapien.ab. or sapien.ti.	192
24	corevalve.ab. or corevalve.ti.	247
25	cribier.ab. or cribier.ti.	39
26	corazon.ab. or corazon.ti.	45
27	revalving.ab. or revalving.ti.	78
28	revalve.ab. or revalve.ti.	1
29	partner trial.ab. or partner trial.ti.	10
30	(tavi or tavr or thv or pavi or pavr or phvr).ab. or (tavi or tavr or thv or pavi or pavr or phvr).ti.	548
31	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	823
32	20 or 31	2023
33	limit 32 to yr="2002 -Current"	1499

7. Centre for Reviews and Dissemination (NHS EED, DARE, HTA) databases (22 Apr 2013)

1	MeSH DESCRIPTOR Aortic Valve Stenosis EXPLODE ALL TREES	38
2	MeSH DESCRIPTOR Aortic Valve EXPLODE ALL TREES	37
3	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES	44
4	MeSH DESCRIPTOR Heart Valve Prosthesis Implantation EXPLODE ALL TREES	63
5	(TAVI):TI OR (transcatheter aortic):TI OR (aortic valve):TI	46
6	#1 OR #2 OR #3 OR #4 OR #5	120

Grey literature searches

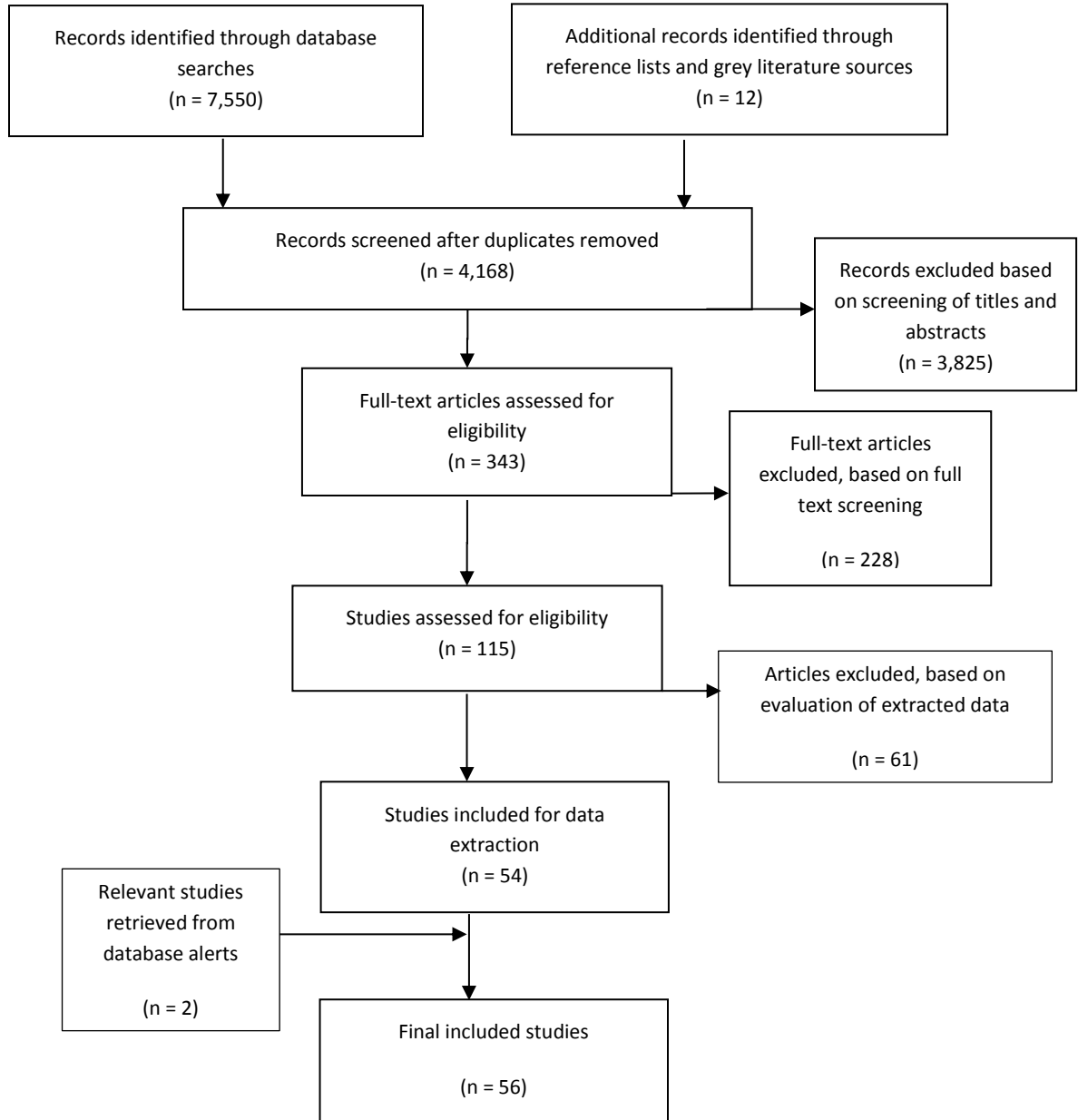
- ClinicalTrials.gov www.clinicaltrials.gov

- National Guideline Clearinghouse www.guideline.gov

- Health Canada Medical Devices Active License Listing (MDALL) database www.mdall.ca
- US Food & Drug Administration (FDA) www.fda.gov
- Google.ca www.google.ca
- valve manufacturer's web sites:
 - a. Edwards SAPIEN™ www.edwards.com
 - b. CoreValve™ www.medtronic.com

Appendix B. PRISMA flow diagram

Figure 12. PRISMA flow diagram of study selection



Appendix B. Excluded studies

Study		Study characteristics					Reasons for exclusion
		Total n	(n) TF	(n) TA	(n) other routes	Study centre	
1	Abdel-Wahab et al. (2011) ¹⁸⁹	662	638	24	-	Germany	Patient overlap in Zahn R. et al. (2011) ¹³⁵
2	Attias et al. (2010) ¹⁹⁰	83	83	NA	-	France	Patient overlap in Thomas et al. (2010) ¹⁴⁰
3	Baan et al. (2012) ¹⁹¹	30	29	NA	1	The Netherlands	Patient overlap in Yong et al. (2012) ¹³¹
4	Bagur et al. (2010) ¹⁹²	213	111	102	-	Canada	Patient overlap in Webb J et al. (2009) ¹²³
5	Bleiziffer et al. (2009) ¹⁹³	227	164	54	-	Germany	Follow-up did not specify approach used
6	Bleiziffer et al. (2009) ¹⁹⁴	137	109	23	5	Germany	Patient overlap in Bleiziffer et al. (2009) ¹¹⁰
7	Bosmans et al. (2011) ¹⁹⁵	328	232	88	-	Belgium	Follow-up did not specify approach used
8	Buellesfeld et al. (2010) ¹⁹⁶	168	155	NA	18	Germany	Patient overlap in Buellesfeld et al. (2011) ¹²²
9	Conradi et al. (2012) ¹⁹⁷	82	22	60	-	Germany	Follow-up did not specify approach used
10	Dager et al. (2012) ¹⁹⁸	53	50	NA	-	Colombia	Patient overlap in Nuis et al. (2012) ¹¹⁸
11	D'Ascenzo et al. (2012) ¹⁹⁹	364	364	NA	-	Italy	Patient overlap in Ussia et al. (2012) ¹²⁶
12	D'Onofrio et al. (2012) ²⁰⁰	566	NA	566	-	Italy	Patient overlap in D'Onofrio et al. (2011) ¹³²
13	D'Onofrio et al. (2011) ²⁰¹	179	NA	179	-	Italy	Patient overlap in D'Onofrio et al. (2011) ¹³²
14	Ducrocq et al. (2010) ²⁰²	54	54	NA	-	France	Patient overlap in Himbert et al. (2009) ²⁰³
15	Dworakowski et al. (2010) ²⁰⁴	151	67	84	-	UK	Patient overlap in Moat et al. (2011) ¹³⁴
16	Godino et al. (2010) ²⁰⁵	137	122	15	-	Italy	Patient overlap in Ussia et al. (2012) ¹²⁶
17	Grube et al. (2008) ²⁰⁶	136	123	NA	13	Germany	Patient overlap in Buellesfeld et al. (2011) ¹²²
18	Grube et al. (2007) ²⁰⁷	86	NA	NA	NA	Germany & Canada	Approach not specified
19	Gurvitch et al. (2011) ²⁰⁸	310	205	105	-	Canada	Patient overlap in Webb et al. (2009) ¹²³

Study		Study characteristics					Reasons for exclusion
		Total n	(n) TF	(n) TA	(n) other routes	Study centre	
20	Gurvitch et al. (2010) ²⁰⁹	70	55	15	-	Canada	Follow-up did not specify approach used
21	Guinot et al (2010) ²¹⁰	90	62	28	-	France	Patient overlap in Thomas et al. (2010) ¹⁴⁰
22	Hayashida et al. (2011) ²¹¹	130	130	NA	-	France	Patient overlap in Thomas et al. (2010) ¹⁴⁰
23	Himbert et al. (2009) ²⁰³	75	51	24	-	France	Patient overlap in Thomas et al. (2010) ¹⁴⁰
24	Jahangiri et al. (2011) ²¹²	63	52	7	4	UK	Patient overlap in Moat et al. (2011) ¹³⁴
25	Kahlert et al. (2009) ²¹³	101	68	33	NA	Germany	Patient overlap in Zahn et al. (2011) ¹³⁵
26	Kapadia et al. (2009) ⁶⁹	18	NR	NR	NR	USA	Approach not specified
27	Lange et al. (2011) ²¹⁴	412	252	127	33	Germany	Follow-up did not specify approach used
28	Motloch et al. (2012) ²¹⁵	84	43	41		Austria	Approach not specified
29	Nuis et al. (2011) ²¹⁶	159	155	5		The Netherlands	Patient overlap in Nuis et al. (2012) ¹¹⁸
30	Nuis et al. (2011) ²¹⁷	150	142	-	8	The Netherlands	Patient overlap in Nuis et al. (2012) ¹¹⁸
31	Pasic M et al. (2010) ²¹⁸	194		194		Germany	Patient overlap in Unbehaun et al. (2011) ¹⁴⁶
32	Petronio et al. (2010) ⁸⁹	514	460	-	54	Italy	Patient overlap in Ussia et al. (2012) ¹²⁶
33	Piazza et al. (2008) ²¹⁹	646	646	-	-	Europe	Patient overlap in Bullesfield (2011) ¹²² and Nuis et al. (2012) ¹¹⁸
34	Piazza et al. (2008) ²²⁰	114	NR	NR	NR	Europe	Approach not specified
35	Pilgrim et al. (2011) ²²¹	256	NR	NR	NR	Switzerland	Approach not specified
36	Rodés-Cabau et al. (2010) ²²²	23	11	12	-	Canada	Patient overlap in Rodés-Cabau et al. (2010) ¹⁴²
37	Rodés-Cabau et al. (2010) ²²³	101	38	63	-	Canada	Focus on myocardial injury only
38	Rodés-Cabau et al. (2012) ¹⁵²	339	168	177	-	Canada	Patient overlap in Rodés-Cabau et al. (2010) ¹⁴²

Table 7. Excluded TAVI studies and reasons for exclusion							
Study		Study characteristics					Reasons for exclusion
		Total n	(n) TF	(n) TA	(n) other routes	Study centre	
39	Roten et al. (2010) ²²⁴	67	NR	NR	NR	Switzerland	Approach not specified
40	Stöhr et al. (2011) ²²⁵	175	82	73	-	Germany	Follow-up did not specify approach used
41	Tamburino et al. (2011) ²²⁶	162	159		3	Italy	Patient overlap in Ussia et al. (2012) ¹²⁶
42	Taramasso et al. (2011) ²²⁷	193	140	16	19	Italy	Patient overlap in Ussia et al. (2012) ¹²⁶
43	Thielmann et al. (2009) ²²⁸	39	15	24	-	Germany	Patient overlap in Thomas et al. (2010) ¹⁴⁰
44	Unbehaun et al. (2012) ²²⁹	358	-	358	-	Germany	Unbehaun et al. (2009) ¹⁴⁶
45	Unbehaun et al. (2012) ²³⁰	258	-	258	-	Germany	Patient overlap in Unbehaun et al. (2011) ¹⁴⁶
46	Unbehaun et al. (2009) ²³¹	175	-	-	-	Germany	Patient overlap in Unbehaun et al. (2011) ¹⁴⁶
47	Van Mieghem et al. (2010) ²³²	99	96	-	3	The Netherlands	Patient overlap in Nuis et al. (2012) ¹¹⁸
48	Walther et al. (2011) ²³³	168	-	168	-	Germany	Patient overlap in Walther et al. (2012) ¹⁴⁵
49	Walther et al. (2011) ²³⁴	150	-	150	-	Germany	Patient overlap in Walther et al. (2012) ¹⁴⁵
50	Walther et al. (2011) ²³⁵	59	-	59	-	Germany	Patient overlap in Walther et al. (2012) ¹⁴⁵
51	Webb J et al. (2011) ²³⁶	253	NR	NR	NR	Canada	Approach not specified
52	Wenaweser et al. (2011) ²³⁷	257	198	55	4	Switzerland	Approach not specified
53	Ye, J. et al. (2009) ²³⁸	13	-	13	-	Canada	Ye J et al. (2010) ¹²⁴
54	Zierer et al. (2008) ²³⁹	26	-	26	-	Germany	Patient overlap in Zierer et al. (2009) ¹¹⁹

Abbreviations: n, patients; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral

Appendix C. Definitions of events

Table 8. Definitions of events		
Events	As defined by authors	Collapsed categories based on consensus
TIA	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} ➤ A fully reversible event in < 24 h without imaging findings^{30,116} ➤ A fully reversible event of short duration¹²³ 	TIA
Minor Stroke	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} ➤ Associated with a modified ranking scale of 0 or 1 at 30 days or longer after the event. Additionally, a NIH stroke scale score of 0 was considered as a minor stroke^{30,116} 	Minor Stroke
Stroke	<ul style="list-style-type: none"> ➤ According to VARC definitions¹²⁵ ➤ A new prolonged event lasting > 24 h or permanent neurological deficit with imaging findings showing an acute ischemic event¹²² ➤ A neurological event lasting > 72 h with imaging findings or CT scans¹²³ 	Major Stroke
Major Stroke	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} ➤ Associated with a modified ranking scale of 2 or greater at 30 days or longer after the event^{30,116} 	Major Stroke
Minor VC	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} ➤ Any event that was not considered a major complication^{30,116} 	Minor VC
VC	<ul style="list-style-type: none"> ➤ Groin problems requiring transfusion¹³⁵ ➤ Aortic dissection, failure of the percutaneous closure device, iliac or femoral rupture or need of blood transfusion¹³⁷ ➤ Aortic rupture, iliofemoral dissection, distal embolization /thrombosis, retroperitoneal hematoma, LV apex bleeding (re-surgery)¹³⁹ ➤ Perforation of the iliac arteries and rupture of the descending aorta¹⁴¹ 	Major VC
Major VC	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} ➤ Any dissection (including thoracic), perforation and rupture resulting in > 3 units of blood, distal embolization (non-cerebral) from a vascular source requiring surgery or leading to an irreversible end-organ damage or nerve injury^{30,116} ➤ Major vascular injury and/or requiring surgery¹³⁴ ➤ Vascular rupture with fatal bleeding or need for urgent vascular surgery or dissection of the aorta¹²³ ➤ Limb-threatening ischemia, vessel rupture requiring surgery and complications of the left ventricle^{120,121} 	Major VC
Minor bleeding	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} (1) bleeding event that did not meet criteria for major bleeding (2) clear site for bleeding (3) loss of hemoglobin > 3 g/dL or loss of hematocrit > 9. Adjustment for transfusions was included at 1 g/dL or 3% for each unit^{30,116} 	Minor bleeding

Table 8. Definitions of events

Events	As defined by authors	Collapsed categories based on consensus
Bleeding	<ul style="list-style-type: none"> ➤ Requiring surgical intervention, blood transfusion, or both¹⁴¹ 	Major bleeding
Major bleeding	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} <ol style="list-style-type: none"> (1) causing death (2) any hospitalisation (3) requiring pericardiocentesis or open and/or endovascular procedure for repair or hemostasis (4) causing permanent disability (5) requiring transfusion of > 3 U within 24 hour period^{30,116} 	Major bleeding
Life threatening bleeding	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} 	Major bleeding
MI	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-127,129,130} ➤ As a clinical MI, not simply periprocedural cardiac marker release¹³⁴ According to the Universal Definition of MI type 5 at time of CABG defined as elevation of cardiac biomarkers > 5 X the 99th percentile of URL together with any of: <ol style="list-style-type: none"> (1) New pathological Q waves or LBBB (2) Imaging evidence of new loss of viable myocardium (3) Angiographically documented coronary occlusion¹³⁴ ➤ 2 X increase in creatine kinase above normal limit, with electrocardiographic evidence of ischemia together with clinical history¹²² ➤ Periprocedural MI was defined as ischemic symptoms or signs combined with elevated cardiac biomarkers (peak value N10× the upper reference limit or a peak value N5× the upper reference limit with new pathologic Q waves in at least 2 contiguous leads) within 72 h after the index procedure¹³⁰ ➤ Elevation of troponin I and/or CK more than 2x above normal with ECG evidence of new ischemia or infarction¹⁴³ 	MI
AKI	<ul style="list-style-type: none"> ➤ According to VARC^{118,125-130} ➤ Chronic dialysis of any sort (hemodialysis, CVVHD, peritoneal) for > 30 days. The date of event was based on the date of the first treatment with renal replacement therapy. Patients who died before 30 days were not considered renal failure events Any episode of renal replacement therapy, either transient or > 30 days duration, was reviewed and assessed for device and procedural relationship^{30,116} ➤ According to the Acute Kidney Injury Network classification¹³⁶ 	AKI

Abbreviations: AKI = acute kidney injury; CABG = coronary artery bypass graft; CK = creatine kinase; CT = computed tomography; CVVHD = continuous venovenous hemodialysis; dL = decilitre; ECG = electrocardiogram; h = hour; LBBB = left bundle branch block; LV = left ventricle; MI = myocardial infarction; NIH = National Institutes of Health; TIA = transient ischemic attack; U = unit; URL = upper reference limit; VARC = Valve Academic Research Consortium; VC = vascular complications

Table 9. Enrollment criteria of included clinical studies		
Study	Inclusion criteria for TAVI	Exclusion criteria for TAVI
Leon et al. (2010) ³⁰	<ul style="list-style-type: none"> - mean gradient > 40 mm Hg or jet velocity > 4.0 m/s of AVA of < 0.8 cm² - symptomatic AS demonstrated by NYHA functional class ≥ II - if the risks of death caused by SAVR outweighed the benefits with a probability of death >50% after surgery, or a serious irreversible condition - life expectancy > 12 months - no iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe calcification, severe tortuosity or vessels size diameter < 7 mm for 22F sheath or < 8mm for 24F sheath. 	<ul style="list-style-type: none"> - left ventricular ejection fraction < 20%; aortic annulus diameter < 18 mm or > 25 mm; severe mitral or aortic regurgitation (grade ≥ 3); - transient ischemic attack or stroke within the previous 6 months; severe renal insufficiency - bicuspid or noncalcified aortic valve; acute myocardial infarction; substantial coronary artery disease requiring revascularization - any invasive cardiac surgery performed 30 days prior to the procedure - pre-existing prosthetic heart valve in any position, prosthetic ring - blood dyscrasias as defined: leukopenia (WBC < 3000 mm³), acute anemia (Hb < 9 mg %), platelet count < 50,000 cells/mm³), history of bleeding diathesis or coagulopathy - untreated clinically significant coronary artery disease requiring revascularization - any emergency surgery - hypertrophic cardiomyopathy with or without obstruction - endocarditis - bulky calcified aortic valve leaflets in close proximity to coronary ostia
Nuis et al. (2012) ¹¹⁸	NR	NR
Ussia et al. (2012) ¹²⁶	<ul style="list-style-type: none"> - patients with severe symptomatic AS with AVA ≤ 1 cm², with no reasonable options for surgery 	
Brito et al. (2012) ¹²⁷	<ul style="list-style-type: none"> - patients unsuitable for or at high risk to undergo SAVR 	
Moat et al. (2011) ¹³⁴	NR	NR
Zahn et al. (2011) ¹³⁵	<ul style="list-style-type: none"> - severe symptomatic AS with AVA ≤ 1 cm² - age ≥ 80 years and a logistic EuroSCORE ≥ 20% or logistic EuroScore < 20% with at least one of the following: cirrhosis, pulmonary insufficiency, porcelain aorta 	<ul style="list-style-type: none"> - no exclusion policy
Buellesfeld et al. (2011) ¹²²	<ul style="list-style-type: none"> - severe AS (0.6 cm²/m²), aortic annulus diameter ranging from 20 to 27 mm as determined by echocardiographic findings. - ascending aorta diameter ≤ 45 mm - age ≥ 75 years or logistic EuroSCORE ≥ 	<ul style="list-style-type: none"> - no exclusion policy

Table 9. Enrollment criteria of included clinical studies		
Study	Inclusion criteria for TAVI	Exclusion criteria for TAVI
	15, or 1 – 2 high risk comorbidities such as: cirrhosis, pulmonary insufficiency, previous cardiac surgery, pulmonary hypertension, porcelain aorta, right ventricular failure or radiation therapy	
Gotzmann et al. (2011) ¹²⁵	- patients with severe symptomatic AS with AVA $\leq 1 \text{ cm}^2$ - patients unsuitable for or at high risk to undergo SAVR	- no exclusion policy
Hammerer et al. (2011) ¹²⁸	- patients with severe symptomatic AS deemed unsuitable to undergo SAVR due to comorbidities	- no exclusion policy
Danenberg et al. (2010) ¹⁴⁴	- excessive high surgical risk or inoperable patients	- no exclusion policy
Yong et al. (2012) ¹³¹	- patients unsuitable for or at high risk to undergo surgery due to older age and comorbidities	- no exclusion policy
Sinning et al. (2010) ¹³⁶	- severe symptomatic aortic stenosis - patients unsuitable for surgery due to perioperative risk	- no exclusion policy
Avanzas et al. (2010) ¹³⁷	- patients with severe symptomatic AS with AVA $\leq 1 \text{ cm}^2$ - aortic annulus diameter ranging from 20 to 27 mm - ascending aorta diameter ≤ 40 (small prosthesis) or ≤ 43 mm (large prosthesis)	- MI in less than 30 days - coronary angioplasty 15 days preceding the procedure or scheduled the month following the procedure - presence of thrombi in left cavities - LVEF $< 20\%$; recent stroke; sepsis or endocarditis; aortic aneurism; coagulopathy or haemorrhagic diathesis; and severe mitral regurgitation
Webb et al. (2009) ¹²³	- patients unsuitable or at high risk to undergo SAVR	- limited quality of life; inclusion in randomized trial
Dewey et al. (2013) ¹³³	- patients with STS risk score $\geq 10\%$ and presence of coexisting comorbidities associated with a mortality risk of $\geq 15\%$ by 30 days postprocedure - mean gradient > 40 mm Hg or jet velocity > 4.0 m/s of AVA of $< 0.8 \text{ cm}^2$ - symptomatic AS with NYHA functional class $\geq \text{II}$	- bicuspid or noncalcified aortic valve; evidence of acute myocardial infarction ≤ 1 month preprocedure; coronary artery disease requiring revascularization - LVEF $< 20\%$; aortic annulus diameter < 8 mm or > 25 mm; severe mitral or aortic regurgitation $> 3+$ - transient ischemic attack or stroke within the previous 6 months - severe renal insufficiency (creatinine > 3.0 mg/dL) or RRT required - endocarditis or sepsis
Walther et al. (2012) ¹⁴⁵	- patients with severe symptomatic AS - age ≥ 75 with increased surgical risk - STS score $> 10\%$, additive EuroSCORE ≥ 9 - patients unsuitable for surgery due to porcelain aorta, chest radiation,	- no exclusion policy

Table 9. Enrollment criteria of included clinical studies		
Study	Inclusion criteria for TAVI	Exclusion criteria for TAVI
D'Onofrio et al. (2011) ¹³²	- patients with logistic EuroSCORE > 20%; STS score > 10% - severe symptomatic AS with AVA < 0.8cm ² - mean transaortic gradient > 40 mm Hg - comorbidities (e.g. porcelain aorta)	- aortic annulus diameter < 18 mm or > 25 mm - life expectancy < 1 year
Unbehaun et al. (2011) ¹⁴⁶	- patients with logistic EuroSCORE ≥ 20 or STS score ≥ 10; unless for specific reasons (e.g., porcelain aorta)	- no exclusion policy
Holzinger et al. (2011) ¹⁴⁷	- patients > 75 years - logistic EuroSCORE > 20%; STS score > 10% - aortic annulus < 25 mm - tricuspid valve and heavily calcified	- bicuspid or non-calcified aortic valve
Strauch et al. (2010) ¹³⁸	- unsuitable for or at high risk to undergo surgery	- no exclusion policy
Ferrari et al. (2010) ¹⁴⁸	- patients with logistic EuroSCORE > 20%	- no exclusion policy
Ye et al. (2010) ¹²⁴	- patients not suitable or at high risk to undergo SAVR due to comorbidities such as ascending porcelain aorta	- no exclusion policy
Zierer et al. (2009) ²⁴⁰	- severe symptomatic AS with AVA ≤ .8 cm ² - logistic EuroSCORE > 20%	- no exclusion policy
Smith et al. (2011) ¹¹⁶	- STS risk score ≥ 10% and presence of coexisting comorbidities associated with a mortality risk of ≥ 15% by 30 days postprocedure - mean gradient > 40 mm Hg or jet velocity > 4.0 m/s of AVA of < 0.8 cm ² - symptomatic AS with NYHA functional class ≥ II	- bicuspid or noncalcified aortic valve; evidence of acute myocardial infarction ≤ 1 month preprocedure; coronary artery disease requiring revascularization; endocarditis or sepsis - LVEF < 20%; aortic annulus diameter < 8 mm or > 25 mm; severe mitral or aortic regurgitation > 3+ - TIA or stroke within the previous 6 months; severe renal insufficiency (creatinine > 3.0 mg/dL) or RRT required
Gillard et al. (2012) ¹²⁹	- severe symptomatic AS with AVA < .8 cm ² ; mean aortic gradient of ≥ 40 mm Hg; jet velocity ≥ 4.0 m/s - symptomatic AS with NYHA functional class ≥ II	- no exclusion policy
Johansson et al. (2011) ¹²⁰	NR	NR
Eltchaninoff et al. (2011) ¹³⁹	- valve area ≤ 1 cm ² or 0.6 cm ² /m ² - NYHA ≥ 2 - logistic EuroSCORE ≥ 20% and/or STS ≥ 10% - porcelain aorta, chest deformation, chest radiation	- life expectancy < 12 months - pre-existing aortic bioprosthesis - MI < 2 weeks preceding the intervention - unprotected > 70% left main coronary artery disease - endocarditis (or history of)

Table 9. Enrollment criteria of included clinical studies		
Study	Inclusion criteria for TAVI	Exclusion criteria for TAVI
		<ul style="list-style-type: none"> - active peptic ulcer or upper gastrointestinal bleeding within 6 months preintervention - infection requiring antibiotic intake - hypersensitivity to aspirin, heparin, ticlopidine or clopidogrel - sensitivity to contrast media
Thomas et al. (2010) ¹⁴⁰	- patient deemed unsuitable for SAVR	- no exclusion policy
Wenaweser et al. (2011) ¹³⁰	<ul style="list-style-type: none"> - severe symptomatic AS with AVA < 1 cm² - logistic EuroSCORE >15% or at least one of the following comorbidities: cirrhosis, pulmonary insufficiency, previous cardiac surgery, porcelain aorta, history of mediastinal radiotherapy, severe connective tissue disease unsuitable for surgery or frailty 	- no exclusion policy
Nielsen et al. (2011) ¹⁴⁹	- patients with severe symptomatic AS with high surgical risk due to age or comorbidities	- no exclusion policy
Ewe et al. (2011) ¹⁴¹	<ul style="list-style-type: none"> - severe symptomatic AS with AVA < 1 cm² - mean aortic pressure gradient ≥ 40 mm Hg 	- no exclusion policy
Rodés-Cabau et al. (2010) ¹⁴²	- patients unsuitable for or at high risk to undergo SAVR	- no exclusion policy
Osten et al. (2010) ¹⁴³	<ul style="list-style-type: none"> - patients not considered candidates for SAVR - severe symptomatic AS with AVA < 1 cm² - mean aortic pressure gradient ≥ 40 mm Hg - at least NYHA class 3 symptoms 	<ul style="list-style-type: none"> - if aortic annulus diameter was <16 or >24 mm - congenital unicuspid or bicuspid valve - untreated proximal coronary artery disease - severe left ventricular dysfunction <20% - Hemodynamic instability requiring inotropic support.
Bleiziffer et al. (2009) ¹¹⁰	- patients unsuitable for or at high risk to undergo SAVR	- no exclusion policy

Table 10. "Procedural success" as defined in individual studies	
Study	Definition of procedural success
Ussia et al. (2012) ¹²⁶	According to VARC ^{xviii}
Brito et al. (2012) ¹²⁷	Idem
Moat et al. (2011) ¹³⁴	Not reported
Zahn et al. (2011) ¹³⁵	Completion of the procedure and lowering of the mean pressure gradient
Buellesfeld et al. (2011) ¹²²	Successful device implantation without occurrence of MACCE ^{xix} during index hospitalisation
Hammerer et al. (2011) ¹²⁸	Reported as device success defined as the implantation of one valve in the proper anatomical position within the aortic annulus without prosthetic valve dysfunction
Danenberg et al. (2010) ¹⁴⁴	No perioperative mortality
Sinning et al. (2010) ¹³⁶	No perioperative mortality or conversion to SAVR
Avanzas et al. (2010) ¹³⁷	The correct implantation and normal functioning of the prosthesis (evaluated by angiography and echocardiogram) without procedural mortality
Walther et al. (2012) ¹⁴⁵	According to VARC
D'Onofrio et al. (2011) ¹³²	Idem
Unbehaun et al. (2011) ¹⁴⁶	Defined as "technical success" without further clarification
Ferrari et al. (2010) ¹⁴⁸	As intraoperative mortality
Gilard et al. (2012) ¹²⁹	According to VARC
Johansson et al. (2011) ¹²⁰	Successful deployment of the valve, retrieval of the catheter, no conversion to conventional surgery and patient exited the intervention room alive
Thomas et al. (2010) ¹⁴⁰	Idem
Wenaweser et al. (2011) ¹³⁰	Defined as device success in the absence of major adverse cardiovascular and cerebral events (MACCEs) during the first 48 hours post-surgery
Nielsen et al. (2011) ¹⁴⁹	As stent valve implantation
Rodés-Cabau et al. (2010) ¹⁴²	The correct implantation and normal functioning of the prosthesis without procedural mortality
Osten et al. (2010) ¹⁴³	Based on valve deployment

^{xviii} (1) successful access, delivery, and deployment of the device and successful retrieval of the delivery system; (2) correct position of the device in the proper anatomic location; (3) intended performance of the prosthetic heart valve (aortic valve area > 1.2 cm² and mean aortic valve gradient < 20 mm Hg or peak velocity < 3 m/s, without moderate or severe prosthetic valve regurgitation); (4) only 1 valve implanted in the proper anatomic location

^{xix} MACCE, major adverse cardiovascular and cerebrovascular events

Appendix D. Tables of included studies

Table 11. Characteristics and descriptions of studies reporting clinical outcomes									
Study	Location	Study design	Enrollment period	n	Access	Valve	Follow-up mean \pm SD (median: IQR)	Oxford level of evidence	Conflict of interest/source of funding
Experimental TF studies									
Leon et al. 2010; ³⁰ Makkar et al. 2012 ³¹	Multicentre CA, USA, GE	RCT	May 2007 – Mar 2009	358	179 TF 179 MM	SAPIEN	1 y, 2 y	1b	Funded by Edwards Lifesciences
Observational TF studies									
Nuis et al. 2012 ¹¹⁸	Multicentre, Colombia & The Netherlands	NRT	Nov 2005 – Jan 2011	358	228 TF 24 AVR 99 MT 7 SC	CoreValve 18 Fr	(10 m:107- 688 d)	4	Funded by Erasmus – Columbus (ERACOL) Latin-European Exchange GRANT
Ussia et al. 2012 ¹²⁶	Multicentre Italian Registry	Case series, prospective	Jun 2007 – Aug 2008	181	172 TF 9 SC	CoreValve 18 Fr	41 \pm 3 m 36 – 51 m	4	Funded by Endotech; 6 of the authors are proctors for the manufacturer
Brito et al. 2012 ¹²⁷	Single centre, Brazil	Case series Prospective	Jan 2007 – Jan 2011	35	34 TF 1 SC	CoreValve 18 Fr	400 \pm 298d	4	No extramural funding to support this study. Two of the authors received financial support from the manufacturer
Moat et al. 2011 ¹³⁴	Multicentre UK TAVI Registry	Case series, prospective	Jan 2007 – Dec 2009	870	599 TF 271 "other routes"	SAPIEN, CoreValve	11 – 46 m	4	4 of the authors are proctors for CV; another 4 are proctors for ES; 2 received funds and grants from both manufacturers and 1 author receives funds and grants from ES
Zahn et al. 2011 ¹³⁵	Multicentre German Registry	Case series, prospective	Jan 2009 – Dec 2009	697	644 TF, 26 TA 22 SC/ 5 Tao	SAPIEN SAPIEN XT, CoreValve18 Fr	1 m	4	No conflict of interest reported/funded by the Foundation Institute of Myocardial Infarction
Buellesfeld et al. 2011 ¹²²	Multicentre Europe & Canada	Case series prospective	2006 - 2008	72 ^{xx}	124 TF 2 SC	CoreValve 18 Fr	2 y	4	Funded by the manufacturer

^{xx} Original number (n=126), moderate risk group (n=54) not included; RCT, randomized controlled trial; NRT, non-randomized NRT trial; TF, transfemoral; TA, transapical; SC, subclavian; m, month; y, year

Table 11. Characteristics and descriptions of studies reporting clinical outcomes									
Study	Location	Study design	Enrollment period	n	Access	Valve	Follow-up mean \pm SD (median: IQR)	Oxford level of evidence	Conflict of interest/source of funding
Gotzmann et al 2011 ¹²⁵	Single centre Germany	Case series Prospective,	Jun 2008 – Sep 2010	150	145 TF 5 SC	CoreValve 18 Fr	6 \pm 1 m	4	Authors declare no extramural funding to support this study
Hammerer et al. 2011 ¹²⁸	Single centre Austria	Case series prospective	Apr 2008–Mar 2010	50	49 TF 1 SC	CoreValve	Mean: 9.9	4	No conflict of interest reported; one of the authors is a trainer for CoreValve™
Danenberg et al. 2010 ¹⁴⁴	Multicentre Israel	Case series prospective	Sep 2008 – Sep 2009	55	52 TF 3 SC	CoreValve	1 m	4	NR
Yong et al. 2012 ¹³¹	Single centre Netherlands	Case series prospective,	Oct 2007–April 2009	119	TF	CoreValve 18 Fr	1 m	4	No conflict of interest reported
Sinning et al. 2010 ¹³⁶	Single centre, Germany	Case series Prospective	NR	77	TF	CoreValve 18 Fr	(9.4: 2 - 15 m)	4	Authors declare no conflict of interest to disclose
Avanzas et al. 2010 ¹³⁷	Multicentre Spain	Case series prospective	Dec 2007 – Jul 2009	108	103 TF 5 SC	CoreValve™	(7.6 m)	4	NR
Webb et al. 2009 ¹²³	Single centre Canada	Case series prospective	Jan 2005 – Nov 2008	168	113 TF 55 TA ¹	Cribier SAPIEN, SAPIEN XT™	(7.4 m)	4	Funded by Edwards Lifesciences, Irvine, California/3 of the authors are consultants to the manufacturer.
Observational TA studies									
Dewey et al. 2013 ¹³³	Multicentre USA	Case series prospective	Sep 2009-Sep 2011	975	TA	SAPIEN	1 y	4	Funded by Edwards Lifesciences
Walther et al. 2012 ¹⁴⁵	Single centre Germany	Case series prospective	Feb 2006 – Jan 2010	299	TA	SAPIEN	(16 m: 3m – 4 y)	4	No conflict of interest reported
D'Onofrio et al. 2011 ¹³²	Multicentre Italian Registry (I-TA)	Case series prospective	Apr 2008–Nov 2010	504	TA	SAPIEN	9.2 \pm 6.5	4	No conflict of interest reported
Unbehaun et al. 2011 ¹⁴⁶	Single centre Germany	Case series prospective	Apr 2008 – Oct 2010	300	TA	SAPIEN	11.7 \pm 8.7m	4	5 of the authors have financial links with the manufacturer

¹ TA pts. excluded for overlapping in Ye J et al. 2010; y, year; m, months;

Table 11. Characteristics and descriptions of studies reporting clinical outcomes									
Study	Location	Study design	Enrollment period	n	Access	Valve	Follow-up mean \pm SD (median: IQR)	Oxford level of evidence	Conflict of interest/source of funding
Holzinger et al. 2011 ¹⁴⁷	Single centre Austria	Case series prospective	Nov 2009 – Dec 2010	22	TA	SAPIEN	(223:19 – 391d)	4	No conflict of interest reported
Strauch et al. 2010 ¹³⁸	Single centre Germany	Case series prospective	Feb 2008 – Jan 2009	30	TA	SAPIEN	8 wk	4	Not reported in this study
Ferrari et al. 2010 ¹⁴⁸	Single centre, Switzerland	Case series prospective	Nov 2008 – Nov 2009	30	TA	SAPIEN	NR	4	The first author has financial links with the manufacturer
Ye et al. 2010 ¹²⁴	Single centre Canada	Case series prospective	Oct 2005 – Feb 2009	71	TA	SAPIEN	12.9 \pm 11.5 m	4	4 of the authors are consultants to the manufacturer and one receives financial support for research from the manufacturer
Zierer et al. 2009 ¹¹⁹	Single centre Germany	matched cohort retrospective	Jan 2006 – Apr 2007	51	21 TA 30 SAVR	SAPIEN	12 \pm 4 m	4	No conflict of interest reported
Experimental TF/TA studies									
Smith et al. 2011; ¹¹⁶ Kodali et al. 2012 ¹¹⁷	Multicentre CA, USA, GE	RCT	May 2007–Mar 2009	699	244 TF 104 TA 351 SAVR	SAPIEN	1 y; 2 y	1 b	Same as above
Observational TF/TA studies									
Gilard et al. 2012 ¹²⁹	Multicentre FRANCE 2 Registry	Case series prospective	Jan 2010 – Oct 2011	3195 ²	2361 TF 567 TA 184 SC	SAPIEN SAPIEN XT Core Valve™	1 y	4	Funded by SAPIEN and CoreValve w/o involvement in data collection or in the analysis of the manuscript
Johansson et al. 2011 ¹²⁰	Single centre Sweden	matched cohort retrospective	Jan 2008 – Nov 2009	40	10 TF 30 TA 40 SAVR	SAPIEN	10 \pm 8 m		One of the authors receives financial benefits from the manufacturer
Elchaninoff et al. 2011 ¹³⁹	Multicentre FRANCE Registry	Case series prospective	Feb 2009 – July 2009	244	161 TF 71 TA 12 SC	SAPIEN; CoreValve	1 m	4	Funded by the French Health Ministry, and by both valve manufacturers
Thomas et al. 2010, ¹⁴⁰ 2011 ¹²¹	Multicentre, UK SOURCE Registry	Case series prospective	Nov 2007 – Jan 2009	1038	463 TF 575 TA	SAPIEN	1 m; 1 y	4	Funded by Edwards Lifesciences, Irvine, California

² Data for 83 patients who underwent transcatheter or transaortic approaches were not provided in the analysis. Data on the type of valve were missing for 43 patients.

Table 11. Characteristics and descriptions of studies reporting clinical outcomes									
Study	Location	Study design	Enrollment period	n	Access	Valve	Follow-up mean \pm SD (median: IQR)	Oxford level of evidence	Conflict of interest/source of funding
Wenaweser et al. 2011 ¹³⁰	Single centre Switzerland	Case series prospective	Aug 2007 – Mar 2010	200	154 TF 43 TA/3 SC	SAPIEN; CoreValve	1 m	4	NR
Nielsen et al. 2011 ¹⁴⁹	Single centre Denmark	Case series prospective	Feb 2006 – Jun 2010	100	24 TF 76 TA	SAPIEN	1 m	4	Authors declare no conflict of interest to disclose
Ewe et al. 2011 ¹⁴¹	Single centre Netherlands	Case series Prospective,	NR	104	45 TF 59 TA	SAPIEN	(12.2m:5.6 – 22m)	4	One author has financial links with Biotronik, BMS Medical Imaging, Boston Scientific, Edwards Lifesciences, GE Healthcare, Medtronic, and St. Jude Medical; another with Biotronik, Boston Scientific, and Medtronic; and 2 others with Edwards Lifesciences
Rodés-Cabau et al. 2010 ¹⁴²	Multicentre Canada,	Case series, prospective	Jan 2005 – Jun 2009	339	162 TF 177 TA	Cribier-Edwards; SAPIEN XT	(8m:3-14m)	4	Seven of the authors are consultants for the manufacturers
Osten et al. 2010 ¹⁴³	Single centre Canada	Case series Prospective	Jan 2007 – May 2009	46	16 TF 30 TA	SAPIEN	7.4 \pm 4.4 m TA 8.3 \pm 5.0 m TF	4	Authors declare no conflict of interest to disclose
Bleiziffer et al. 2009 ¹¹⁰	Single centre Germany	Case series Prospective,	Jun 2007-Feb 2009	203	153 TF 50 TA	SAPIEN CoreValve	6 m	4	NR

Abbreviations: TF, transfemoral; TA, transapical; SC, subclavian; TAO, transaortic; RCT, randomized control trial; MT, medical therapy; SAVR, surgical aortic valve replacement, gp, group; EG, early group; LG, late group

¹ Five pts underwent TAVI via the subclavian artery, 4 via mini sternotomy, and 3 were converted to SAVR.

Table 12. Patient characteristics at baseline															
Study	Group (n)	Age in years ± SD, Male %	STS score	Logistic Euro SCORE ± SD	Prior stroke or TIA n (%)	Porcelain aorta n (%)	Prior Pace maker	Chronic Kidney disease n (%)	Coronary artery disease	Prior COPD n (%)	Pulmonary hypertension	Prior PCI n (%)	Prior CABG n (%)	Prior Cardiac Surgery	Peripheral vascular disease
Experimental TF Studies															
Leon et al. 2010 ³⁰	179 TF	83.1 ± 8.6 46%	11.2 ± 5.8	26.4±17	48 (27.4)	34 (19.0)	22.9%	10 (5.6)	121 (68)	74 (41.3)	42.4%	30.5%	37.4%	Excluded	54 (30.3)
	179 MM	82.3± 8.3 47%	12.1±6.1	30.4±19	46 (27.)	20 (11)	19.5%	17 (9.6)	133 (74)	94 (52.5)	43.8%	24.8%	45.6%	Excluded	45(25)
Observational TF Studies															
Nuis al. 2012 ¹¹⁸	235	80 ± 7 49%	6.1±5.5	19±13.7	NR	NR	26 (11)	11 (5)	NR	78 (33)	NR	60 (26)	54 (23)	NR	30 (13)
	24 SAVR	78 ± 9 54%	4.1±2.4	10.1±4.3	NR	NR	3 (13)	1 (5)	NR	5 (21)	NR	5 (21)	0	NR	6 (25)
	99 MM	80 ± 8 42%	5.8±3.8	19±12.1	NR	NR	10 (10)	0 (0)	NR	16 (16)	NR	26 (26)	21 (21)	NR	28 (28)
Ussia et al 2012 ¹²⁶	181	81±6.1 44.2%	11.4± 9.9	24±13.5	8 (4.4)	39 (215)	16 (8.8)	52 (28.7)	96 (53.0)	34 (18.8)	NR	51 (28.2)	34 (18.8)	NR	27 (14.9)
Brito et al. 2012 ¹²⁷	35	81.5 ± 9 46%	14.5 ± 11.6	18.4 ± 14.3	5 (14.3)	NR	3 (8.6)	21 (60)	14 (40)	8 (22.8)	NR	8 (22.8)	5 (14.30)	2 (5.7)	6 (17.1)
Moat et al. 2011 ¹³⁴	599	81.7 ± 7.4 52%	NR	17.1 ^{xxi} (11-25)	NR	NR	NR	5.4%	43.4%	27.5%	NR	NR	27.3%	NR	19.5%
Zahn et al. 2011 ¹³⁵	697	81.4±6.3 44.2%	NR	20.5± 13.2	7.8%	10%	NR	61.5%	60%	171 (24.6)	62.8%	34.2%	21.5%	3.0%	30.3%
Buellesfeld et al. 2011 ¹²²	72 ^{xxii}	80.8 ± 7.2 47%	NR	29 ± 14.5	17 (23.6)	9 (12.5)	6 (8.3)	36 (50)	54 (75)	19 (26.4)	34 (47.2)	20 (27.8)	28 (38.9)	NR	17 (23.6)
Gotzmann et al. 2011 ¹²⁵	150	79.1±6.4 NR	NR	21 ± 16.2	NR	NR	NR	NR	NR	NR	91 (63)	NR	NR		NR
Hammerer et al. 2011 ¹²⁸	50	80.6±5.9 34%	6.2±3.8	24.9± 16.3	4 (8)	NR	6 (12)	NR	23 (46)	NR	15 (30)	5 (10)	6 (12)	NR	11 (22)
Danenberg et al. 2010 ¹⁴⁴	55	81.5 ± 7.1 36%	NR	19.3±8.1	NR	9 (17)	NR	NR	24 (43.6)	22 (40)	NR	NR	NR	NR	NR

^{xxi} Median

^{xxii} Moderate-risk group (n=54) not included in this review

Table 12. Patient characteristics at baseline															
Study	Group (n)	Age in years ± SD, Male %	STS score	Logistic Euro SCORE ± SD	Prior stroke or TIA n (%)	Porcelain aorta n (%)	Prior Pace maker	Chronic Kidney disease n (%)	Coronary artery disease	Prior COPD n (%)	Pulmonary hypertension	Prior PCI n (%)	Prior CABG n (%)	Prior Cardiac Surgery	Peripheral vascular disease
Yong et al. 2012 ¹³¹	119	80.7 ± 7.8 47%	6.1 ± 4.5	18.5 ± 12.7	NR	NR	NR	NR	21 (18)	40 (34)	NR	35 (29)	15 (13)	NR	21 (18)
Sinning et al. 2010 ¹³⁶	77	88.8 ± 6.7 48%	9.3 ± 6.1	31.2 ± 17.6	20 (26)	NR	NR	48 (62)	50 (65)	20 (26)	32 (42)	37 (48)	8 (10)	NR	35 (46)
Avanzas et al. 2010 ¹³⁷	108	78.6 ± 6.7 45.4%	NR	16 ± 13.9	NR	NR	NR	18 (16.7)	36 (33.3)	NR	NR	15 (13.9)	NR	NR	NR
Webb ¹ et al. 2009 ¹²³	113	85* 65%	8.7	25	16 (14.2)	20 (17.7)	15 (13.3)	14 (12.4)	73 (64.6)	25 (22.1)	28 (24.8)	NR	41 (36.3)	NR	18 (15.9)
Observational TA Studies															
Dewey et al. 2013 ¹³³	975 TA	84.8 ± 6.2 47.3%	12.1 ± 4.6	27.6 ± 16.7	295 (30.3)	NR	NR	NR	NR	437 (44.8)	361 (37)	458 (47)	494 (51)	NR	600 (61.5)
Walther et al. 2012 ¹⁴⁵	299 TA	82 ± 6.4 30%	12 ± 8	31 ± 16	56 (18.7)	39 (13)	NR	8 (2.5)	159 (53.2)	129 (87)	80 (26.8)	NR	NR	86 (28.8)	142 (47.5)
D'Onofrio et al. 2011 ¹³²	504 TA	81.2 ± 6.5 39.3%	11 ± 4	26.3 ± 13.8	39 (7.7)	108 (21.4)	NR	24 (4.8)	254 (50.4)	173 (34.3)	49 (9.7)	111 (22)	72 (14.3)	83 (16.5)	229 (45.4)
Unbehaun et al. 2011 ¹⁴⁶	300 TA	79.6 ± 8.1 32.3%	19.1 ± 15.5	38.5 ± 19.4	80 (26.7)	16 (5.3)	29 (9.7)	NR	178 (59)	137 (45.7)	113 (38)		49 (16.3)	17 (5.7)	208 (69.3)
Holzinger et al. 2011 ¹⁴⁷	22 TA	80 ± 6.9 36.3%	14.3 ± 4.5	24.8 ± 6.5	2 (9)	4 (18)	NR	NR	7 (31)	2 (9)	7 (31)	5 (22)	NR	7 (31)	NR
Strauch et al. 2010 ¹³⁸	30 TA	82.1* (71-88) 37%	13.6 (3.2-26)	19 (5-77.4)	NR	NR	NR	2 (6.7)	19 (63)	NR	NR	NR	NR	NR	NR
Ferrari et al. 2010 ¹⁴⁸	30 TA	80.1 ± 8.7 50%	NR	32.2 ± 13.3	4 (13.3)	2 (6.6)	NR	12 (40)	11 (36.7)	NR	NR	NR	NR	4 (13.3)	21 (70)
Ye et al. 2010 ¹²⁴	71 TA	80 ± 8.1 38%	12.1 ± 7.7	34.5 ± 20.4	22 (31)	15 (21.1)	13 (18.3)	NR	53 (74.6)	20 (28.2)	42 (60)	NR	31 (44)	NR	NR

¹ Only the TF group included in the analysis, the TA group overlaps with Ye, J. et al. 2010; *Median

Table 12. Patient characteristics at baseline															
Study	Group (n)	Age in years ± SD, Male %	STS score	Logistic Euro SCORE ± SD	Prior stroke or TIA n (%)	Porcelain aorta n (%)	Prior Pace maker	Chronic Kidney disease n (%)	Coronary artery disease	Prior COPD n (%)	Pulmonary hypertension	Prior PCI n (%)	Prior CABG n (%)	Prior Cardiac Surgery	Peripheral vascular disease
Zierer et al. 2009 ¹¹⁹	21 TA	85 ± 6 29%	NR	38±14	3 (14)	3 (14)	NR	4 (19)	9 (43)	7 (33)	6 (29)	NR	NR	3 (14)	4 (19)
	30 SAVR	82 ± 4 37%	NR	35±9	1 (5)	1 (5)	NR	3 (10)	11 (37)	10 (33)	7 (23)	NR	NR	0	7 (23)
Experimental TF/TA Studies															
Smith ^{xxiii} et al. 2011 ¹¹⁶	248 SAVR	84.4±6.7 57.8%	11.7±3.3	29.1±16.1	25.4%	2 (0.4)	21.9%	9.5%	365(74.6)	211(42.9)	40.3%	31.5%	39.4%	Excluded	34.9%
	244 TF	84.4±6.7 57.8%	11.7±3.3	29.1±16.1	25.4%	2 (0.4)	21.9%	9.5%	365(74.6)	211(42.9)	40.3%	31.5%	39.4%	Excluded	34.9%
	104 TA	83.2±6.5 55.8%	11.8±3.5	29.8±15.9	35.7%	1.9%	18.6%	7.9%	78.9%	44%	37.6%	37.8%	52.9%	Excluded	60.2%
	103 SAVR	83.2±6.5 55.8%	11.8±3.5	29.8±15.9	35.7%	1.9%	18.6%	7.9%	78.9%	44%	37.6%	37.8%	52.9%	Excluded	60.2%
Observational TF/TA Studies															
Gilard et al. 2012 ¹²⁹	2361 TF	83± 7.2 47.4%	14.5±11.9	21.2±14.7	9.60%	5.50%	NR	2.6%	44.4%	NR	20%	NR	15.2%	1.6%	12.50%
	567 TA	81.5±7.4 58.6%	15.1±13.8	24.8±14.7	11%	1.8%	NR	3.1%	59.4%	NR	16.8%	NR	30%	1.5%	48.1%
Johansson et al. 2011 ¹²⁰	10 TF	83±6 50%	NR	25.6 ± 15	1 (10)	0	NR	1 (10)	NR	1 (10)	0	5 (50)	4 (40)	0	5 (50)
	30 TA	80±6 50%	NR	23.5±17	4 (13)	8 (27)	NR	1 (3)	NR	12 (40)	4 (13)	11 (37)	5 (17)	1 (3)	14(47)
	40 SAVR	81±5 45%	NR	22.7 ± 16	4 (10)	NA	NR	3 (33)	NR	12 (30)	1 (3)	NA	NA	N/A	17(43)

^{xxiii} Data obtained from the Supplementary Appendix Table 4, % values are based on group characteristics for TF + SAVR (n =492) and TA + SAVR (n = 207) respectively

Table 12. Patient characteristics at baseline															
Study	Group (n)	Age in years ± SD, Male %	STS score	Logistic Euro SCORE ± SD	Prior stroke or TIA n (%)	Porcelain aorta n (%)	Prior Pace maker	Chronic Kidney disease n (%)	Coronary artery disease	Prior COPD n (%)	Pulmonary hypertension	Prior PCI n (%)	Prior CABG n (%)	Prior Cardiac Surgery	Peripheral vascular disease
Eltchaninoff et al. 2011 ¹³⁹	161 TF	82.9±6.8 47%	20.0± 12.8	25.2± 11.2	9.90%	NR	17.4	NR	38.50%	NR	NR	NR	23.6	NR	4.3
	71 TA	82.1±7.3 64.3%	18.4±12	26.8± 11.6	20 (28.2)	NR	4 (5.6)	NR	33 (46.5)	NR	NR	NR	28.2%	NR	NR
Thomas et al. 2010 ¹⁴⁰	463 TF	81.7±6.7 50%	NR	25.7± 14.5	NR	21 (4.5)	NR	118 (25.5)	220 (47.5)	NR	114 (24.6)	NR	81 (17.5)	NR	49 (10.6)
	575 TA	80.7±7.0 44.2%	NR	29.1± 16.3	NR	65 (11.3)	NR	187 (32.5)	317 (55.1)	NR	172 (30)	NR	155 (27)	NR	161 (28)
Wenaweser ^{xxiv} et al. 2011 ¹³⁰	154 TF	83.1 ± 4.8 61%	6.4± 4.7	24.2± 15.6	15 (9.5)	NR	NR	NR	91 (58)	NR	NR	32 (20)	29 (18.5)	NR	30 (19)
	46 TA	78.1±9.6 55.8%	6.3±5.5	26.1± 14.3	3 (7)	NR	NR	NR	34 (79)	NR	NR	12 (28)	11 (25.6)	NR	19 (39.5)
Nielsen et al. 2011 ¹⁴⁹	24 TF	83.2 ± 7.6 45.8%	NR	15.9 ± 9.4	2 (8)	NR	NR	NR	NR	7 (29)	NR	NR	NR	37 (49)	NR
	76 TA	80.6±6.7 44.4%	NR	21.5± 13.5	9 (12)	NR	NR	NR	NR	21 (28)	NR	NR	NR	5 (21)	NR
Ewe et al. 2011 ¹⁴¹	45 TF	82.2±7.1 46.7%	8.5±3.8	20.1± 11.7	4.4%	0	4.4%	22.2%	NR	24.4%	NR	NR	33.3%	NR	11.1%
	59 TA	79.4 ± 8.3 52.5%	8.9±3.5	22.6± 11.9	17%	6.8%	8.5%	22.0%	NR	28.8%	NR	NR	42.4%	NR	67.8%
Rodés-Cabau et al. 2010 ¹⁴²	162 TF	83 ± 8 56%	9.0 ± 5.8	NR	27 (17)	28 (17)	NR	86 (53)	110 (68)	45 (28)	35 (21.6)	47 (29)	49 (30)	NR	31 (19)
	177 TA	80±8 61%	10.5±6.9	NR	50 (28)	33 (19)	NR	104 (59)	124 (70)	55 (31)	49 (27.7)	52 (29.4)	67 (38)	NR	89 (50.3)

^{xxiv} Some of the patients in this study may overlap with Thomas et al. 2010, 2011;

*Plus-minus values are mean ± SD; NYHA denotes New York Heart Association; MT Medical Therapy; TAVI denotes transcatheter aortic valve implantation; SAVR aortic valve replacement; PCI percutaneous coronary intervention; CABG coronary-artery bypass; COPD chronic obstructive pulmonary disease; PVD peripheral vascular disease; IHD Ischemic Heart Disease; PH pulmonary hypertension; NR not reported, NA not applicable

Table 12. Patient characteristics at baseline															
Study	Group (n)	Age in years ± SD, Male %	STS score	Logistic Euro SCORE ± SD	Prior stroke or TIA n (%)	Porcelain aorta n (%)	Prior Pace maker	Chronic Kidney disease n (%)	Coronary artery disease	Prior COPD n (%)	Pulmonary hypertension	Prior PCI n (%)	Prior CABG n (%)	Prior Cardiac Surgery	Peripheral vascular disease
Osten et al. 2010 ¹⁴³	16 TF	82 ± 9 62%	7.2%	24.1%	1 (6)	1 (6)	NR	NR	13 (81)	2 (13)	7 (44)	6 (38)	5 (31)	NR	7 (44)
	30 TA	79±7 34%	9.5%	25.9%	3 (10)	9 (30)	NR	NR	20 (67)	10 (33)	6 (20)	11 (37)	12 (40)	NR	13 (43)
Bleiziffer et al. 2009 ¹¹⁰	153 TF	81.4 ± 6.7 52%	6.5±4.1	22.1±13.6	24 (16)	NR	NR	31 (20)	78 (51)	35 (23)	34 (22)	NR	NR	25 (16)	26 (17)
	50 TA	81.5±5.9 22%	6.3±3.8	22.0±14.9	4 (8)	NR	NR	10 (20)	33 (50)	6 (12)	14 (28)	NR	NR	9 (18)	26 (52)

*Plus-minus values are mean ± SD; NYHA denotes New York Heart Association; MT Medical Therapy; TAVI denotes transcatheter aortic valve implantation; SAVR aortic valve replacement; PCI percutaneous coronary intervention; CABG coronary-artery bypass; COPD chronic obstructive pulmonary disease; PVD peripheral vascular disease; IHD Ischemic Heart Disease; PH pulmonary hypertension; NR not reported, NA not applicable

Comparative studies	TAVI (n) STS (\pm SD)*		Control (n) STS (\pm SD)		P value
	TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	179 (11.2 \pm 5.8%)	-	179 (12.1 \pm 6.1%)	-	0.14 ^a
Nuis et al. 2012 ¹¹⁸	235 (6.1 \pm 5.5%)	-	MM (NR)	24 (4.1 \pm 2.4%)	0.17
Zierer et al. 2009 ¹¹⁹	-	-	-	-	-
Johansson et al. 2011 ¹²⁰	-	-	-	-	-

* Plus-minus values are mean \pm SD; MM, medical management; SAVR, surgical aortic valve replacement
^a p-value reported by the authors

Comparative studies	TAVI (n) (\pm SD)		Control (n) (\pm SD)		P value
	TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	179 (26.4 \pm 17.2%)	-	179 (30.4 \pm 19.1%)	-	0.04 ^a
Nuis et al. 2012 ¹¹⁸	235 (19.1 \pm 13.7%)	-	-	24 (10.1 \pm 4.3%)	
Zierer et al. 2009 ¹¹⁹	-	21 (38 \pm 14%)	-	30 (35 \pm 9%)	0.4
Johansson et al. 2011 ¹²⁰	10 (25.6 \pm 15)	-	-	40 (22.7 \pm 16)	0.6
	-	10 (23.5 \pm 17)	-	40 (22.7 \pm 16)	0.9

* Plus-minus values are mean \pm SD;

^a p value obtained from Leon et al., 2010

Table 15. Feasibility outcomes				
Study n (%)	Group (n)	Procedural Success	Valve-in- valve	Conversion to SAVR
Experimental TF studies				
Leon et al. 2010 ³⁰	179 TF	NR	3 (1.7)	0
	179 MT	NA	NA	3 (1.7)
Nuis et al. 2012 ²⁴¹	235 TF	NR	NR	1 (0.42)
	AVR 24	NR	NR	0
	99 MT	NA	NA	NA
Ussia et al. 2012 ¹²⁶	181	166 (92)	8 (4.4)	2 (1.1)
Brito et al. 2012 ¹²⁷	35	29 (83)	2 (5.8)	0
Moat et al. 2011 ¹³⁴	599	583 (97.3)	7 (1.2)	0
Zahn et al. 2011 ¹³⁵	697	686 (98.4)	NR	5 (0.7)
Buellesfeld et al. 2011 ¹²²	72	53 (72.6)	NR	NR
Gotzmann et al. 2011 ¹²⁵	150	NR	5 (3.3)	2 (1.3)
Hammerer et al. 2011 ¹²⁸	50	47 (94)	NR	0
Danenberg et al. 2010 ¹⁴⁴	55	54 (98)	NR	0
Yong et al. 2012 ¹³¹	119	NR	1 (1)	NR
Sinning et al. 2010 ¹³⁶	77	75 (97)	3 (4)	1 (1)
Avanzas et al. 2010 ¹³⁷	108	106 (98)	1 (0.92)	2 (1.8)
Webb et al. 2009 ¹²³	113	NR	NR	0
Observational TA studies				
Dewey et al. 2013 ¹³³	975	NR	NR	NR
Walther et al. 2012 ¹⁴⁵	299	274 (91.5*)	15 (5)	6 (2)
D'Onofrio et al. 2011 ¹³²	504	499 (99)	3 (0.6)	1 (0.2)
Unbehaun et al. 2011 ¹⁴⁶	300	299 (99.7)	10 (3.3)	3 (1)
Holzinger et al. 2011 ¹⁴⁷	22	NR	NR	2 (9)
Strauch et al. 2010 ¹³⁸	30	NR	NR	2 (7)
Ferrari et al. 2010 ¹⁴⁸	30	29 (97)	1 (3.3)	1 (3.3)
Ye et al. 2010 ¹²⁴	71	NR	2 (2.8)	1 (1.4)
	21	NR	0	2 (10)
Zierer et al. 2009 ¹¹⁹	30 SAVR	NR	NA	NA
Experimental TF/TA studies				
Smith et al. 2011 ¹¹⁶	248 SAVR	NR	NR	NA
	244 TF	NR	NR	NR
	104 TA	NR	NR	NR

* Data obtained from Kempfer et al 2011 on same population

Table 15. Feasibility outcomes				
Study n (%)	Group (n)	Procedural Success	Valve-in-valve	Conversion to SAVR
	103 SAVR	NR	NR	NA
Observational TF/TA studies				
Gilard et al. 2012 ¹²⁹	2361 TF	2293 (97)	47 (2.0)	16 (0.7)
	567 TA	544 (96)	16 (2.9)	4 (0.7)
Johansson et al. 2011 ¹²⁰	10 TF	10 (100)	0	0
	30 TA	28 (93)	1 (0.3)	1 (0.3)
	40 SAVR	NR	NR	0
Eltchaninoff et al. 2011 ¹³⁹	161 TF	NR ^b	NR	NR
	71 TA	NR ^b	NR	NR
Thomas et al. 2010 ¹²¹	463 TF	95%	3 (0.6)	8 (1.7)
	575 TA	93%	19 (3.3)	20 (3.5)
Wenaweser et al. 2011 ¹³⁰	157 TF	95.5%	4 (3.1)	NR
	43 TA	93%	0	NR
Nielsen et al. 2011 ¹⁴⁹	24 TF	88%	NR	NR
	76 TA	93%	NR	NR
Ewe et al. 2011 ¹⁴¹	45 TF	NR ^c	NR	NR
	59 TA	NR ^c	NR	NR
Rodés-Cabau* et al. 2010 ¹⁴²	162 TF	90.5%	4 (2.4)	2 (1.2)
	177 TA	96.1%	5 (2.8)	4 (2.3)
Osten et al. 2010 ¹⁴³	16 TF	88%	NR	0
	30 TA	93%	NR	1 (3.3)

^b Global procedural success rate including TA & TF was 98.3%

^c Global procedural success rate including TA & TF was 92.5%

* A total of 345 (TF 168 / TA 177) procedures was performed in 339 patients

Table 16. Operative outcomes				
Study	Group (n)	Procedural Time \pm SD	Length of ICU/CCU stay, days \pm SD	Length of hospital stay, days \pm SD
Experimental TF studies				
Leon et al. 2010 ³⁰	179 TF	NR	4 \pm 7*	6.1 \pm 5.4*
	179 MT	NA	NR	NR
Observational TF studies				
Ussia et al. 2012 ¹²⁶	181	68.6 \pm 28.7	NR	NR
Brito et al. 2012 ¹²⁷	35	NR	NR	11 \pm 12.5
Zahn et al. 2011 ¹³⁵	697	86.1 \pm 47	2 (1-3)*	17.2 \pm 9.2
Hammerer et al. 2011 ¹²⁸	50	NR	NR	18 \pm 5
Yong et al. 2012 ¹³¹	119	80 \pm 23	NR	NR
Sinning et al. 2010 ¹³⁶	77	63 \pm 25	NR	NR
Webb ^{xxv} et al. 2009 ¹²³	113	NR	NR	5 (3-9)*
Observational TA studies				
Walther et al. 2012 ¹⁴⁵	299	89 \pm 46.5 ^a	NR	NR
D'Onofrio et al. 2011 ¹³²	504	NR	2*	9 \pm 4
Holzinger et al. 2011 ¹⁴⁷	22	108 \pm 22	NR	18 \pm 5
Strauch et al. 2010 ¹³⁸	30	NR	4.1 \pm 0.6	12.1 \pm 0.8
Ferrari et al. 2010 ¹⁴⁸	30	116 \pm 31.4	2.4 \pm 4	15.1 \pm 10.2
Zierer et al. 2009 ¹¹⁹	21	154 \pm 33	1 \pm 0.4	5 \pm 0.9
	30 SAVR	208 \pm 28	3.2 \pm 1.9	12 \pm 3.4
Experimental TF/TA studies				
Smith et al. 2011 ¹¹⁶	248 SAVR	230 \pm 46	5.6 \pm 6.7 ^b	10.8 \pm 10.2 ^b
	244 TF	133 \pm 89	3.3 \pm 6 ^b	6.9 \pm 7.8 ^b
	104 TA	133 \pm 89	6.6 \pm 8.9 ^b	8.1 \pm 7 ^b
	103 SAVR	230 \pm 46	8 \pm 11 ^b	8.1 \pm 6.2 ^b
Observational TF/TA studies				
Gilard et al. 2012 ¹²⁹	2361 TF	NR	NR	10.5 \pm 8.1
	567 TA	NR	NR	13.3 \pm 7.8
Wenaweser et al. 2011 ¹³⁰	157 TF	91.4 \pm 39	NR	NR
	43 TA	81 \pm 31	NR	NR
Nielsen et al. 2011 ¹⁴⁹	24 TF	NR	NR	8.6 \pm 3.3
	76 TA	NR	NR	9.6 \pm 7.3
Ewe et al. 2011 ¹⁴¹	45 TF	71 (58-98)*	NR	6 (5-7)*
	59 TA	64 (49-80)*	NR	6 (5-8)*
Osten et al. 2010 ¹⁴³	16 TF	NR	NR	10:3-21*
	30 TA	NR	NR	10:5-47*
Bleiziffer et al. 2009 ¹¹⁰	153 TF	76.4 \pm 34.4	NR	NR
	50 TA	95.4 \pm 26.1	NR	NR

* Data extracted from Reynolds et al. 2013 "Results of the PARTNER Trial Cohort B", calculations based on n=175 TF

^{xxv} TA group excluded due to overlap with Ye et al. 2010

^b Data extracted from Reynolds et al. 2012 "Results of the PARTNER Trial Cohort A"; calculations based on n=101 TA-AVR, n=91 SAVR; n=234 TF-AVR, n=221 SAVR

Table 17. Periprocedural causes of death at day three

Study (%)	Group (n)	Peri-procedural mortality	VC	HF/multi-organ failure	Arrhythmia	Valve-related mortality	MI	Stroke
Experimental TF studies								
Leon et al. 2010 ³⁰	179	1.1	NR	NR	NR	NR	NR	NR
	179 MM	NR	-	-	-	-	-	-
Observational TF studies								
Nuis et al. 2012 ²⁴¹	235	2.5	1.27 ^{xxvi}	0.42	0.85	0	0	0
	24 SAVR	NR	-	-	-	-	-	-
Brito et al. 2012 ¹²⁷	35	11.2	8.4	0	0	0	2.8	0
Gotzmann et al. 2011 ¹²⁵	150	2	NR	NR	NR	NR	NR	NR
Hammerer et al. 2011 ¹²⁸	50	2	2	0	0	0	0	0
Danenberg et al. 2010 ¹⁴⁴	55	3.6	3.6	0	0	0	0	0
Sinning et al. 2010 ¹³⁶	77	1.3	0	1.3	0	0	0	0
Avanzas et al. 2010 ¹³⁷	108	0	0	0	0	0	0	0
Webb et al. 2009 ¹²³	113	3.6	3.6 ^{xxvii}	0	0	0	0	0
Observational TA studies								
Holzinger et al. 2011 ¹⁴⁷	22	0	0	0	0	0	0	0
Strauch et al. 2010 ¹³⁸	30	0	0	0	0	0	0	0
Ferrari et al. 2010 ¹⁴⁸	30	3.3	3.3	0	0	0	0	0
Ye et al. 2009 ¹²⁴	71	2.8	0	1.4	0	1.4	0	0
Zierer et al. 2009 ¹¹⁹	21 TA	5	0	0	0	5	0	0
	30 SAVR	0	-	-	-	-	-	-
Observational TF/TA studies								
Johansson et al. 2011 ¹²⁰	10 TF	0	0	0	0	0	0	0
	30 TA	0	0	0	0	0	0	0
Eltchaninoff et al. 2011 ¹³⁹	161 TF	3.1	NR	NR	NR	NR	NR	NR
	71 TA	7.0	NR	NR	NR	NR	NR	NR
Nielsen et al. 2011 ¹⁴⁹	24 TF	8.3	8.3	0	0	0	0	0
	76 TA	2.6	0	2.6	0	0	0	0
Ewe et al. 2011 ¹⁴¹	45 TF	6.7	6.7	0	0	0	0	0
	59 TA	3.4	0	0	0	1.7	1.7	0
Rodés-Cabau et al. 2010 ¹⁴²	162 TF	1.9	NR	NR	NR	NR	NR	NR
	177 TA	1.7	NR	NR	NR	NR	NR	NR
Osten et al. 2010 ¹⁴³	16 TF	0	0	0	0	0	0	0
	30 TA	3.3	3.3	0	0	0	0	0
Bleiziffer et al. 2009 ¹¹⁰	153 TF	2	2	0	0	0	0	0
	50 TA	6	0	0	0	0	0	0

^{xxvi} Including 1 bleeding event

^{xxvii} Including 2 bleeding events

Table 18. Periprocedural mortality in comparative studies					
Comparative studies	TAVI (n) Mortality %		Control (n) Mortality %		P value
	TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	(179) 1.1	-	(179) NR	-	-
Nuis et al. 2012 ¹¹⁸	(235) 2.5	-	(MM) NR	(24) NR	-
Zierer et al. 2009 ¹¹⁹	-	(21) 5	-	(30) 0	0.41
Johansson et al. 2011	(10) 0	(30) 0	-	NR	-

Abbreviations: MM, medical management; NR, not reported TF, transfemoral; TA, transapical

Table 19. All-cause, cardiac death and relative causes at 30 days

Study	Group (n)	All cause	Cardiac total	CHF/ multi-organ failure	Arrhythmia	Sudden	Vascular complication	Valve related	MI
Experimental TF studies									
Leon et al. 2010 ³⁰	179 TF	9 (5)	5 (2.8)	2 (1.1)	0	1 (0.65)	2 (1.1)	0	0
	179 MM	5 (2.8)	3 (1.7)	1 (0.6)	1 (0.6)	1 (0.6)	NA	NA	0
Observational TF studies									
Nuis et al. 2012 ¹¹⁸	235 TF	20 (8.5)	11 (4.7)	6 (2.6)	0	2 (0.85)	3 (1.3)	0	0
	AVR 24	2 (8)	2 (8)	0	1 (4)	0	0	1 (4)	0
Ussia et al. 2012 ¹²⁶	181	20 (11)	10 (5.5)	7 (3.9)	0	0	3 (1.7)	0	0
Brito et al. 2012 ¹²⁷	35	4 (11.4)	4 (11.4)	0	0	0	4 (11.4)	0	0
Moat et al. 2011 ¹³⁴	599	33 (5.5)	NR	NR	NR	NR	NR	NR	NR
Zahn et al. 2011 ¹³⁵	697 ^{xxviii}	86 (12.4)	NR	NR	NR	NR	NR	NR	NR
Buellesfeld et al. 2011 ¹²²	72 ^{xxix}	14 (19.4)	8 (11)	NR	NR	NR	NR	NR	NR
Gotzmann et al. 2011 ¹²⁵	150	12 (8.3)	NR	NR	NR	NR	NR	NR	NR
Hammerer et al. 2011 ¹²⁸	50	4 (8)	4 (8) ^{xxx}	NR	NR	NR	1 (2)	NR	NR
Danenberg et al. 2010 ¹⁴⁴	55	3 (5.4)	2 (3.6)	0	0	0	2 (3.6)	0	0
Yong al. 2012 ¹³¹	119	15 (13)	6 (5)	6 (5)	0	0	0	0	0
Sinning et al. 2010 ¹³⁶	77	8 (10.3)	NR	NR	NR	NR	NR	NR	NR
Avanzas et al. 2010 ¹³⁷	108	8 (7.4)	6 (5.8)	1 (0.9)	0	0	2 (1.9)	3 (2.9)	0
Webb ^{xxxi} et al. 2009 ¹²³	113	9 (8)	7 (6.2)	3(2.7)	1 (0.9)	1 (0.9)	2 (1.9)	0	0
Observational TA studies									
Dewey et al. 2013 ¹³³	975	86 (8.8)	NR	NR	NR	NR	NR	NR	NR
Walther et al. 2012 ¹⁴⁵	299	26 (8.7)	14 (4.7)	NR	NR	NR	NR	NR	NR
D'Onofrio et al. 2011 ¹³²	504	42 (8.3)	22 (4.4)	15 (3)	5 (1)	0	2 (0.4)	0	0
Unbehaun et al. 2011 ¹⁴⁶	300	14 (4.7)	9 (3)	9 (3.0)	0	0	0	0	0
Holzinger et al. 2011 ¹⁴⁷	22	0	0	0	0	0	0	0	0
Strauch et al. 2010 ¹³⁸	30	4 (13)	4 (13)	4 (13)	0	0	0	0	0

xxviii Including 26 TA, 22 TS and 5TAO procedures

xxix Not including moderate risk group

xxx Two cardiac deaths were not specified and 1 was due to unknown causes

xxxi TA group excluded due to overlap with Ye et al. 2010

Table 19. All-cause, cardiac death and relative causes at 30 days

Study	Group (n)	All cause	Cardiac total	CHF/ multi-organ failure	Arrhythmia	Sudden	Vascular complication	Valve related	MI
Ferrari et al. 2010 ¹⁴⁸	30	3 (10)	2 (6.6)	1 (3.3)	0	0	1 (3.3)	0	0
Ye et al. 2010 ¹²⁴	71	12 (16.9)	5 (5.6)	3 (4.2)	0	0	1 (1.4)	1 (1.4)	0
Zierer et al. 2009 ¹¹⁹	21	3 (15)	3 (15)	2 (10)	0	0	0	1 (5)	0
	30 SAVR	3 (10)	2 (6.6)	1 (3.3)	0	0	1 (3.3)	0	0
Experimental TF/TA studies									
Smith et al. 2011 ¹¹⁶	248 SAVR	15 (6.1)	7 (3.0)	NR	NR	NR	NR	NR	NR
	244 TF	8 (3.3)	8 (3.3)	NR	NR	NR	NR	NR	NR
	104 TA	4 (3.8)	3 (2.9)	NR	NR	NR	NR	NR	NR
	103 SAVR	7 (6.8)	3 (3.0)	NR	NR	NR	NR	NR	NR
Observational TF/TA studies									
Gilard et al. 2012 ¹²⁹	2361 TF	190 (8.5)	132 (6)	NR	NR	NR	NR	NR	NR
	567 TA	77 (13.9)	59 (11)	NR	NR	NR	NR	NR	NR
Johansson et al. 2011 ¹²⁰	10 TF	2 (20)	0	1 (10)	0	0	0	0	0
	30 TA	2 (6.7)	1(3.3)	1(3.3)	0	0	0	0	0
	40 SAVR	NR	NR	NR	NR	NR	NR	NR	NR
Eltchaninoff et al. 2011 ¹³⁹	161 TF	18 (11)	NR	NR	NR	NR	NR	NR	NR
	71 TA	12 (17)	NR	NR	NR	NR	NR	NR	NR
Thomas et al. 2010 ¹²¹	463 TF	29 (6.3)	NR	NR	NR	3 (0.6)	NR	NR	NR
	575 TA	59 (10.3)	NR	NR	NR	2 (0.3)	NR	NR	NR
Wenaweser et al. 2011 ¹³⁰	157 TF	11 (7)	9 (5.7)	NR	NR	NR	NR	NR	NR
	43 TA	4 (9.3)	4 (9.3)	NR	NR	NR	NR	NR	NR
Nielsen et al. 2011 ¹⁴⁹	24 TF	3 (12.5)	3 (12.5)	0	0	0	3 (12.5)	0	0
	76 TA	5 (6.6)	5 (6.6)	2 (2.6)	0	0	2 (2.6)	0	1 (1.3)
Ewe et al. 2011 ¹⁴¹	45 TF	5 (11)	5 (11)	2 (4.4)	0	0	0	0	0
	59 TA	5 (8.5)	4 (6.8)	1 (1.7)	0	0	2 (3.4)	1 (1.7)	0
Rodés-Cabau et al. 2010 ¹⁴²	162 TF	16 (9.5)	NR	NR	NR	NR	NR	NR	NR
	177 TA	20 (11.3)	NR	NR	NR	NR	NR	NR	NR
Osten et al. 2010 ¹⁴³	16 TF	1 (6)	1 (6)	0	0	0	0	1 (6)	0
	30 TA	2 (6.6)	2 (6.6)	1 (3.3)	0	0	0	0	0
Bleiziffer et al. 2009 ¹¹⁰	153 TF	17 (11)	10 (6.5)	NR	NR	NR	2 (1.4)	5 (3.3)	NR
	50 TA	4 (8)	2 (4)	1 (2)	0	0	0	1 (2)	0

Table 20. Non-cardiac and related causes of death at 30 days

Study n (%)	Group (n)	Non-Cardiac total	Stroke	Renal failure	Respiratory causes	Infection/sepsis	Others ¹
Experimental TF studies							
Leon et al. 2010 ³⁰	179 TF	4 (2.2)	2 (1.1)	0	0	1 (0.65)	1 (0.6)
	179 MM	2 (1.1)	0	0	0	2 (1.1)	0
Observational TF studies							
	235 TF	9 (3.6)	3 (1.3)	0	2 (0.85)	2 (0.85)	2 (0.85)
Nuis et al. 2012 ¹¹⁸	24 AVR	0	0	0	0	0	0
Ussia et al. 2012 ¹²⁶	181	10 (5.5)	3 (1.6)	1 (0.6)	3 (1.6)	0	3 (1.6)
Brito et al. 2012 ¹²⁷	35	0	0	0	0	0	0
Moat et al. 2011 ¹³⁴	599 TF	NR	-	-	-	-	-
Zahn et al. 2011 ¹³⁵	697 ²	NR	-	-	-	-	-
Buellesfeld et al. 2011 ¹²²	72	6 (8.3)	NR	NR	NR	NR	NR
Gotzmann et al. 2011 ¹²⁵	150	NR	-	-	-	-	-
Hammerer et al. 2011 ¹²⁸	50	0	0	0	0	0	0
Danenberg et al. 2010 ¹⁴⁴	55	1 (1.8)	1 (1.8)	0	0	0	0
Yong al. 2012 ¹³¹	119	9 (8.0)	3 (2.5)	NR	3 (2.5)	3 (2.5)	NR
Sinning et al. 2010 ¹³⁶	77	NR	-	-	-	-	-
Avanzas et al. 2010 ¹³⁷	108	2 (1.8)	0	0	1 (0.9)	1 (0.9)	0
Webb et al. 2009 ¹²³	113 TF	2 (1.8)	2 (1.8)	0	0	0	0
Observational TA studies							
Dewey et al. 2013 ¹³³	975	NR	-	-	-	-	-
Walther et al. 2012 ¹⁴⁵	299	12 (4)	0	0	6 (2)	3 (1)	3 (0.7)
D'Onofrio et al. 2011 ¹³²	504	20 (4)	6 (1.2)	0	0	8 (1.6)	6 (1.2)
Unbehaun et al. 2011 ¹⁴⁶	300	5 (1.5)	0	0	0	1 (0.3)	4 (1.3)
Holzinger et al. 2011 ¹⁴⁷	22	0	0	0	0	0	0
Strauch et al. 2010 ¹³⁸	30	0	0	0	0	0	0
Ferrari et al. 2010 ¹⁴⁸	30	1 (3.3)	0	0	1 (3.3)	0	0
Ye et al. 2010 ¹²⁴	71	7 (9.8)	0	0	3 (4.2)	0	4 (5.6)

¹ Including liver failure, cancer, mesenteric ischemia, abdominal complications, vein thrombosis and ischemia

² Including 26 TA, 22 TS and 5Tao procedures

Table 20. Non-cardiac and related causes of death at 30 days							
Study	Group (n)	Non-Cardiac total	Stroke	Renal failure	Respiratory causes	Infection/sepsis	Others¹
n (%)							
Zierer et al. 2009 ¹¹⁹	21	0	0	0	0	0	0
	30 SAVR	1 (3.3)	0	0	1 (3.3)	0	0
Experimental TF/TA							
Smith et al. 2011 ¹¹⁶	248 SAVR	8 (3.2)	NR	NR	NR	NR	NR
	244 TF	0 (0.0)	NR	NR	NR	NR	NR
	104 TA	1 (1.0)	NR	NR	NR	NR	NR
	103 SAVR	4 (3.9)	NR	NR	NR	NR	NR
Observational TF/TA							
Gilard et al. 2012 ¹²⁹	2361 TF	58 (2.5)	NR	NR	NR	NR	NR
	567 TA	18 (3.2)	NR	NR	NR	NR	NR
Johansson et al. 2011 ¹²⁰	10 TF	1(10)	0	0	0	0	1 (10)
	30 TA	1 (3.3)	0	0	0	0	1 (3.3)
	40 SAVR	NR	-	-	-	-	-
Eltchaninoff et al. 2011 ¹³⁹	161 TF	NR	-	-	-	-	-
	71 TA	NR	-	-	-	-	-
Thomas et al. 2010 ¹²¹	463 TF	NR	-	-	-	-	-
	575 TA	NR	-	-	-	-	-
Wenaweser et al. 2011 ¹³⁰	157 TF	2 (1.3)	NR	NR	NR	NR	NR
	43 TA	0	0	0	0	0	0
Nielsen et al. 2011 ¹⁴⁹	24 TF	0	0	0	0	0	0
	76 TA	0	0	0	0	0	0
Ewe et al. 2011 ¹⁴¹	45 TF	0	0	0	0	0	0
	59 TA	1 (1.7)	1 (1.7)	0	0	0	0
Rodés-Cabau et al. 2010 ¹⁴²	162 TF	NR	-	-	-	-	-
	177 TA	NR	-	-	-	-	-
Osten et al. 2010 ¹⁴³	16 TF	0	0	0	0	0	0
	30 TA	0	0	0	0	0	0
Bleiziffer et al. 2009 ¹¹⁰	153 TF	10 (6.5)	NR	NR	NR	NR	NR
	50 TA	2 (4)	NR	NR	NR	NR	NR

Table 21. All-cause, cardiac and non-cardiac mortalities for comparative studies at 30 days						
Comparative studies	Outcomes	TAVI (n) Mortality %		Control (n) Mortality %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	All causes	(179) 5.0	-	(179) 2.8	-	0.4 ^a
	Cardiac	(179) 2.8	-	(179) 1.7	-	0.72
	Non-cardiac	(179) 2.2	-	(179) 1.1	-	0.68
Smith et al. 2011 ¹¹⁶	All causes	(244) 3.3	-	-	(248) 6.2	0.13 ^b
		-	(104) 3.8	-	(103) 7.0	0.32 ^b
	Cardiac	(244) 3.3	-	-	(248) 3.0	0.85 ^b
		-	(104) 2.9	-	(248) 3.0	0.95 ^b
	Non-cardiac	(244) 0.0	-	-	(248) 3.2	0.01
		-	(104) 0.9	-	(103) 4.0	0.21
Nuis et al. 2012 ¹¹⁸	All causes	(235) 8.5	-	NR	(24) 8.0	1.0
	Cardiac	(235) 4.7	-	-	(24) 8.0	0.3
	Non-cardiac	(235) 3.6	-	-	(24) 0	1.0
Zierer et al. 2009 ¹¹⁹	All causes	-	(21) 15	-	(30) 10	0.5
	Cardiac	-	(21) 15	-	(30) 6.6	0.3
	Non-cardiac	-	21 0.0	-	(30) 3.3	1.0
Johansson et al. 2011 ¹²⁰	All causes	(10) 20	(30) 6.6	-	NR	-
	Cardiac	(10) 10	(30) 3.3	-	NR	-
	Non-cardiac	(10) 10	(30) 3.3	-	NR	-

^a p value obtained from Leon et al. 2010

^b P value obtained from Smith et al. 2011, Supplementary Appendix

Table 22. All cause/cardiac mortality and related causes at one year

Study n (%)	Group (n)	All cause	Cardiac total	CHF/ multi- organ failure	Arrhy- thmia	Sudden	Vascular compli- cation	Valve related	MI	Endo- carditis
Experimental TF studies										
Leon et al. 2010 ³⁰	179	71 (40)	39 (22) ^a	10 (5.6)	0	4 (2.3)	5 (2.8)	NR	1 (0.6)	2 (1.1)
	179 MM	107 (60)	85 (47.5) ^b	31(17.2)	2 (1.1)	18 (10)	0	NR	0	0
Observational TF studies										
Ussia et al. 2012 ¹²⁶	181	42 (23.2)	15 (8.3) ^c	9 (5.2)	0	1 (0.6)	3 (7.1)	0	0	0
Sinning et al. 2010 ¹³⁶	77	20 (26)	5 (6.5)	4 (5.2)	0	0	0	0	1 (1.3)	0
Observational TA studies										
Zierer et al. 2009 ¹¹⁹	21	5 (24)	4 (16.7)	3 (14.3)	0	0	0	1 (4.5)	0	0
	30 SAVR	5 (17)	4 (13.3)	2 (6.7)	0	1 (3.3)	1 (3.3)	0	0	0
Experimental TF/TA studies										
Smith et al. 2011 ¹¹⁶	248 SAVR	62 (26.4)	29 (13.3)	NR	NR	NR	NR	NR	NR	NR
	244 TF	54 (22.2)	29 (12.6)	NR	NR	NR	NR	NR	NR	NR
	104 TA	30 (29)	18 (18.5)	NR	NR	NR	NR	NR	NR	NR
	103 SAVR	27 (27.9)	11 (12.3)	NR	NR	NR	NR	NR	NR	NR

^a Including 18 unknown TF deaths; data extracted from the Supplementary Appendix

^b Including 33 unknown and 1 "other" cardiovascular death; data extracted from the Supplementary Appendix

^c Including 2 unknown deaths

Table 23. Non-cardiac mortality and related causes at one year

Study n (%)	Group (n)	Non-cardiac total ^a	Stroke	Renal failure	Respiratory causes	Infection /sepsis	Bleeding/aneurysm	Cancer	Liver failure	Others
Experimental TF studies										
Leon et al. 2010 ³⁰	179 TF	31 (17.3)	4 (2.2)	3 (1.7)	NR	9 (5.0)	0 (0.0)	4 (2.2)	NR	11 (6.1) ^b
	179 MM	22 (12.3)	4 (2.2)	1 (0.6)	NR	7 (3.9)	2 (1.1)	4 (2.2)	NR	4 (2.2)
Observational TF studies										
Ussia, 2012 ¹²⁶	181	27 (15)	6 (3.3)	3 (1.7)	9 (5)	1 (0.6)	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)
Sinning et al. 2010 ¹³⁶	77	15 (19.4)	1 (1.3)	7 (9.1)	7 (9.1)	0	0	0	0	0
Observational TA studies										
Zierer et al. 2009 ¹¹⁹	21	1 (4.8)	0	0	1 (4.8)	0	0	0	0	0
	30	1 (3.3)	0	0	1 (3.3)	0	0	0	0	0
Experimental TF/TA studies										
Smith et al. 2011 ¹¹⁶	248 SAVR	33 (13.1)	NR	NR	NR	NR	NR	NR	NR	NR
	244 TF	25 (9.6)	NR	NR	NR	NR	NR	NR	NR	NR
	104 TA	12 (10.5)	NR	NR	NR	NR	NR	NR	NR	NR
	103 SAVR	16 (15.6)	NR	NR	NR	NR	NR	NR	NR	NR

^a Where possible, mortality was recalculated using the definitions applied in this analysis.

^b Including 2 accidentals, 8 “others” and 1 unknown non-cardiac causes

Table 24. All cause, cardiac and non-cardiac mortality for comparative studies at one year						
Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		Mortality %		Mortality %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	All causes [‡]	(179) 39.6	-	(179) 59.8	-	<0.001
	Cardiac	(179) 22.3	-	(179) 47.5	-	<0.001
	Non cardiac	(179) 17.3	-	(179) 12.3	-	0.18
Smith et al. 2011 ¹¹⁶	All causes	(244) 22.2	-	-	(248) 26.4	0.29 ^h
		-	(104) 29.0	-	(103) 27.9	0.85 ^h
	Cardiac	(244) 12.6	-	-	(248) 13.3	0.83 ^h
		-	(104) 18.5	-	(103) 12.3	0.24 ^h
	Non cardiac	(244) 9.6	-	-	(248) 13.1	0.22
		-	(104) 10.5	-	(103) 15.6	0.29
Zierer et al. 2009 ¹¹⁹	All causes	-	(21) 24	-	(30) 17	0.39
	Cardiac	-	(21) 19		(30) 13.5	0.7
	Non cardiac	-	(21) 5.0		(30) 3.3	1.0

Abbreviations: MM, medical management; SAVR, surgical aortic valve replacement

[‡] Data obtained from Leon et al. 2010, Supplementary Appendix reported as "> 30 days"

^h P value obtained from Smith et al., 2011, Supplementary Appendix

Table 25. All cause, cardiac and non-cardiac mortalities from 30 days to one year						
Comparative studies	Outcomes	TAVI (n) Mortality %		Control (n) Mortality %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	All causes ^{xxxii}	(179) 34.6	-	(179) 57.0	-	<0.001
	Cardiac	(179) 19.5	-	(179) 45.8	-	<0.001
	Non cardiac	(179) 15.1	-	(179) 11.2	-	0.27
Smith et al. 2011 ¹¹⁶	All causes	(244) 18.9	-	-	(248) 20.2	NS
		-	(104) 25.2	-	(103) 20.9	NS
	Cardiac	(244) 9.3	-	-	(248) 10.3	NS
		-	(104) 15.6	-	(103) 9.3	NS
	Non cardiac	(244) 9.6	-	-	(248) 9.9	NS
		-	(104) 9.6	-	(103) 11.6	NS
Zierer et al. 2009 ¹¹⁹	All causes	-	(21) 10	-	(30) 6.8	NS
	Cardiac	-	(21) 5.0	-	(30) 6.8	NS
	Non cardiac	-	(21) 5.0	-	(30) 0.0	NS

Abbreviations: MM, medical management; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

^{xxxii} Data obtained from Leon et al., 2010, Supplementary Appendix

Table 26. All-cause, cardiac and non-cardiac mortality at two years

Study n (%)	Group (n)	All-cause mortality	Cardiac total	Non-cardiac total
Experimental TF studies				
Makkar et al. 2012 ³¹	179 TF	77 (43.3)	50 (31)	27 (12.3)
	179 MM	117 (68.0)	100 (62.4)	17 (5.6)
Observational TF studies				
Buellesfeld 2011 ¹²²	72	33 (45.8)	19 (26.4)	14 (19.4)
Experimental TF/TA studies				
Kodali ^a et al. 2012 ¹¹⁷	248 SAVR	80 (34.6)	42 (20.6)	38 (14)
	244 TF	74 (30.9)	43(19.5)	31 (11.4)
	104 TA	42 (41.1)	24 (26.0)	18 (15.1)
	103 SAVR	34 (35.7)	17 (20.5)	17 (15.2)

^a Data reported from Kodali et al., Supplementary Appendix

Table 27. Mortality for comparative studies at two years						
Comparative studies	Outcomes	TAVI (n) Mortality %		Control (n) Mortality %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	All causes	(179) 43.3	-	(179) 68	-	<0.001 ^{xxxiii}
	Cardiac	(179) 31.0	-	(179) 62.4	-	<0.001 ^h
	Non cardiac	(179) 12.3	-	(179) 5.6	-	0.12
Kodali et al. 2011 ¹¹⁷	All causes	(244) 30.9	-	-	(248) 34.6	0.38 ^{xxxiv}
		-	(104) 41.1	-	(103) 36	0.44 ^l
	Cardiac	(244) 19.5	-	-	(248) 20.6	0.79 ^l
		-	(104) 26.0	-	(103) 20	0.40 ^l
	Non cardiac	(244) 11.4	-	-	(248) 14.0	0.31
		-	(104) 15.1	-	(103) 16	0.98

Abbreviations: MM, medical management; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral

^{xxxiii} P value obtained from Makkar et al. 2012

^{xxxiv} P value obtained from Kodali et al. 2012, Supplementary Appendix; All percentages are Kaplan-Meier estimates which do not differ from the actual raw data had censored data not occurred

Table 28. Mortality for comparative studies from one to two years						
Comparative studies	Outcomes	TAVI (n) Mortality %		Control (n) Mortality %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	All causes	(179) 3.7	-	(179) 8.2	-	0.07
	Cardiac	(179) 10.2	-	(179) 13.2	-	0.32
	Non cardiac	(179) 6.5	-	(179) 5.0	-	0.50
Kodali et al. 2011 ¹¹⁷	All causes	(244) 8.7	-	-	(248) 8.2	0.87
		-	(104) 12.1	-	(103) 8.1	0.26
	Cardiac	(244) 6.9	-	-	(248) 7.3	0.90
		-	(104) 7.5	-	(103) 7.7	0.98
	Non cardiac	(244) 1.8	-	-	(248) 0.9	0.45
		-	(104) 4.6	-	(103) 0.8	0.21

Table 29. All-cause, cardiac and non-cardiac causes of death at three years

Study n (%)	Group (n)	All-cause mortality	Cardiac total ¹	CHF/multi- organ failure	Arrhy- thmia	Sudden death	Valve related	MI	Endo- carditis
Observational TF studies									
Ussia et al. 2012 ¹²⁶	181	62 (34.2)	15 (8.2)	11 (6.1)	NR	1 (0.6)	NR	NR	NR

¹ Including 3 unknown deaths

Table 30. Periprocedural complications at day three

Study (%)	Group (n)	Vascular complications and Bleeding ^{xxxv}					Stroke	AKI		Arrhythmia	MI	PPM
		Major VC	Minor VC	Major B	Minor B	VC & B Total		RRT				
Experimental TF studies												
Leon et al. 2010 ³⁰	179 TF	NR	NR	NR	NR	NR	1.7	NR	NR	NR	NR	
Ussia et al. 2012 ¹²⁶	181	3.3	NR	6.1	22.1	9.4	NR	NR	NR	4.5	NR	
Brito et al. 2012 ¹²⁷	35	20.0	0	31.4	0	51.4	0	NR	NR	0	NR	
Zahn et al. 2011 ¹³⁵	697	6.3	2.4	4.0	13.1	10.3	2.8	NR	NR	0.3	39.3	
Gotzmann et al. 2011 ¹²⁵	150	2.7	8.7	NR	NR	2.7	2.7	NR	NR	0.7	NR	
Hammerer et al. 2011 ¹²⁸	50	10.0	14.0	6.0	10	16	4.0	2.0	NR	0	14	
Danenberg et al. 2010 ¹⁴⁴	55	NR	0	NR	NR	16.3	0	NR	NR	NR	NR	
Yong et al. 2012 ¹³¹	119	NR	NR	NR	NR	-	NR	NR	NR	17	NR	
Avanzas et al. 2010 ¹³⁷	108	9.3	2.8	1.0	0	10.3	0	NR	NR	1.0	35.2	
Webb et al. 2009 ¹²³	113	9.8	NR	NR	NR	9.8	NR	NR	NR	NR	NR	
Observational TA studies												
Walther et al. 2012 ^{xxxvi145}	299	NR	NR	2.0	0	2.0	0.7	NR	NR	NR	4.0	
D'Onofrio et al. 2011 ¹³²	504	4.8	0	0.8	0	5.6	NR	NR	NR	1.6	NR	
Holzinger et al. 2011 ¹⁴⁷	22	NR	NR	4.5	0	4.5	0	NR	NR	NR	0	
Ferrari et al. 2010 ¹⁴⁸	30	NR	NR	6.6	0	6.6	0	0	0	0	0	
Ye et al. 2010 ¹²⁴	71	1.4	NR	NR	0	1.4	NR	NR	NR	NR	NR	
Zierer et al. 2009 ¹¹⁹	21	10.0	0	10	0	20	0	0	0	NR	0	
Experimental TF/TA studies												
Smith et al. 2011 ¹¹⁶	244 TF	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR
	104 TA	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR
Observational TF/TA studies												

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy; B, bleeding; TF, transfemoral; TA, transapical; NR, not reported;

^{xxxv} Also considered as vascular complications according to VARC definitions, thus 1 patient may have more than 1 event

^{xxxvi} One case of endocarditis reported

Table 30. Periprocedural complications at day three

Study (%)	Group (n)	Vascular complications and Bleeding ^{xxxv}					VC & B Total	Stroke	AKI		Arrhythmia	MI	PPM
		Major VC	Minor VC	Major B	Minor B	RRT			AKI				
Johansson et al. 2011 ¹²⁰	10 TF	10	0	10	NR	10 ^a	NR	0	0	NR	0		
	30 TA	3.3	0	NR	NR	3.3	NR	6.7	NR	NR	0		
Eltchaninoff et al. 2011 ¹³⁹	161 TF	16	0	NR	NR	16	NR	NR	NR	NR	NR		
	71 TA	2.8	0	NR	NR	2.8	NR	NR	NR	NR	NR		
Thomas et al. 2010 ¹²¹	463 TF	NR	NR	10	0	10	NR	NR	NR	NR	NR		
	575 TA	NR	NR	9	0	9	NR	NR	NR	NR	NR		
Wenaweser et al. 2011 ¹³⁰	157 TF	1.3	NR	NR	NR	1.3	NR	NR	NR	0	NR		
	43 TA	0	NR	NR	NR	0	NR	NR	NR	NR	NR		
Nielsen et al. 2011 ¹⁴⁹	24 TF	4.2	0	NR	NR	4.2	0	NR	NR	0	NR		
	76 TA	1.3	NR	NR	NR	1.3	1.3	NR	NR	3.9	NR		
Ewe et al. 2011 ¹⁴¹	45 TF	20	0	NR	NR	2.2	NR	NR	NR	NR	NR		
	59 TA	5.1	0	NR	NR	5.1	NR	NR	NR	NR	NR		
Rodés-Cabau et al. 2010 ¹⁴²	162 TF	13.1	0	NR	NR	13.1	0.6	NR	7.1	0.6	NR		
	177 TA	13	0	NR	NR	13	0.6	NR	9	1.1	NR		
Osten et al. 2010 ¹⁴³	16 TF	6.2	0	NR	0	6.2	0	NR	NR	0	NR		
	30 TA	10	0	NR	0	10	0	NR	NR	0	NR		
Bleiziffer et al. 2009 ¹¹⁰	153 TF	16	0	NR	NR	16	NR	NR	NR	NR	NR		
	50 TA	6	0	10	0	16	NR	NR	NR	NR	NR		

^a Same patient for both of the 2 events

Table 31. Clinical complications at 30 days

Study	n (%)	Group (n)	Vascular complications				Neurological events			AKI		Arrhythmia	MI	PPM	Endocarditis
			Major VC	Minor VC	Major Bleeding	Minor Bleeding	Major stroke	Minor stroke	TIA	Stage 3	RRT				
Experimental TF studies															
Leon et al. 2010 ³⁰	179 TF	29 (16)	26 (14.5)	30 (17)	NR	9 (5)	3 (1.7)	0	0	2 (1.1)	1 (0.6)	0	6 (3.4)	0	
	179 MT	2 (1.1)	7 (3.9)	7 (3.9)	NR	2 (1.1)	1 (0.6)	0	1 (0.6)	3 (1.7)	2 (1.1)	0	9 (5.0)	0	
Observational TF studies															
Nuis et al. 2012 ¹¹⁸	235	24 (10)	18 (8)	21 (9)	46 (20)	11 (5)	NR	NR	5 (2)	NR	9 (5)	3 (1.3)	48 (20)	NR	
	24 SAVR	0	0	2 (8)	0	2 (8)	1 (4.0)	NA	2 (8)	NR	2 (11)	1 (4)	1 (4)	NR	
	99 MT	NA	NA	NA	NA	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Ussia et al. 2012 ¹²⁶	181	6 (3.3)	0	34 (19)	40 (22)	5 (2.8)	0	NR	16 (6.7)	4 (2.2)	NR	9 (5.1)	22 (12.1)	NR	
Brito et al. 2012 ¹²⁷	35	7 (20)	5 (14.3)	31.4	0	2 (5.7)	0	0	0	0	NR	0	9 (32.1)	0	
Moat et al. 2011 ¹³⁴	599	50 (8.4)	0	NR	NR	24 (4)	0	NR	NR	NR	NR	6 (1.0)	NR [‡]	NR	
Zahn et al. 2011 ¹³⁵	697	130 (19.4)	16 (2.4)	27 (4.0)	88 (13.1)	19 (2.8)	0	0	NR	NR	1 (0.15)	2 (0.3)	262 (37.6)	NR	
Buellesfeld et al. 2011 ¹²²	72	NR	NR	NR	NR	6 (8.3)	0	2 (2.8)	NR	NR	NR	4 (5.6)	33 (46)	0	
Gotzmann et al. 2011 ¹²⁵	150	4 (2.7)	13 (8.7)	NR	NR	4 (2.7)	0	NR	2 (1.3)	3 (2)	NR	1 (0.7)	72 (48)	NR	
Hammerer et al. 2011 ¹²⁸	50	5 (10)	7 (14)	3 (6)	5 (10)	2 (4)	NR	NR	1 (2)	1 (2)	NR	0	7 (14)	NR	
Danenberg et al. 2010 ¹⁴⁴	55	12 (22)	0	2 (3.6)	0	0	0	1 (1.8)	2 (3.6)	NR	0	0	20 (37)	NR	
Yong et al. 2012 ¹³¹	119	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	20 (17)	21 (18)	NR	
Sinning et al. 2010 ¹³⁶	77	NR	NR	NR	NR	NR	NR	NR	12 (9.6)	8 (10.4)	NR	NR	NR	NR	
Avanzas et al. 2010 ¹³⁷	108	10 (9.3)	3 (2.8)	1 (0.9)	0	0	0	NR	NR	NR	NR	1 (0.9)	38 (35.2)	NR	
Webb et al. 2009 ¹²³	113	11 (9.8)	0	13 (11.6)	0	6 (5.3)	0	NR	5 (4.4)	0	NR	NR	5 (4.4)	NR	
Observational TA studies															
Dewey et al. 2013 ¹³³	975	NR	NR	NR	NR	2.2	0	NR	NR	NR	NR	NR	NR	NR	
Walther et al. 2012 ¹⁴⁵	299	NR	NR	6 (2)	0	2 (0.7)	0	NR	NR	45 (15)	NR	NR	12 (4)	1 (0.4)	
D'Onofrio et al. 2011 ¹³²	504	24 (4.8)	0	4 (0.8)	0	15 (3)	0	NR	NR	30 (6.1)	NR	8 (1.6)	27 (5.3)	NR	
Unbehaun et al. 2011 ¹⁴⁶	300	6 (4.2)	0	NR	NR	3 (1)	0	NR	NR	NR	NR	NR	19 (6.3)	2 (0.67)	
Holzinger et al. 2011 ¹⁴⁷	22	4 (18)	0	1 (4.5)	NR	1 (4.5)	0	NR	NR	2 (9.1)	NR	NR	0	NR	

[‡] 16.3% when including "other routes" (n=867)

Table 31. Clinical complications at 30 days

Study	n (%)	Group (n)	Vascular complications				Neurological events			AKI		Arrhythmia	MI	PPM	Endocarditis
			Major VC	Minor VC	Major Bleeding	Minor Bleeding	Major stroke	Minor stroke	TIA	Stage 3	RRT				
Strauch et al. 2010 ¹³⁸		30	NR	NR	NR	NR	NR	NR	NR	11 (37)	6 (20)	NR	NR	NR	NR
Ferrari et al. 2010 ¹⁴⁸		30	1 (3.3)	0	2 (6.6)	0	1 (3.3)	0	NR	0	0	NR	0	0	NR
Ye et al. 2010 ¹²⁴		71	1 (1.4)	0	1 (1.4)	2 (2.8)	1 (1.4)	0	NR	NR	NR	NR	NR	6 (8.5)	NR
Zierer et al. 2009 ¹¹⁹		21	2 (10)	NR	2 (10)	0	0	0	NR	NR	0	0	NR	0	0
		30 SAVR	0	NR	1 (3)	0	1 (3)	0	NR	NR	3 (10)	3 (10)	NR	1 (3)	1 (3)
Experimental TF/TA studies															
Smith et al. 2011 ^{116†}		248 SAVR	7 (2.9)	1 (0.4)	49 (20)	0	4 (1.7)	0	0	3 (1.2)	5 (2.1)	41 (16.5)	1 (0.4)	8 (3.4)	0
		244 TF	34 (14)	21 (8.6)	23 (9.5)	0	7 (2.9)	2 (0.8)	3 (1.3)	4 (1.7)	6 (2.5)	18 (7.4)	0	9 (3.7)	0
		104 TA	4 (3.8)	0	9 (8.7)	0	6 (5.8)	1 (1.1)	0	0 (0)	4 (3.9)	12 (11.5)	0	4 (3.9)	0
		103 SAVR	5 (5)	1 (1)	18 (18)	1 (1)	3 (3.2)	1 (1.1)	1 (1.1)	1 (1)	5 (5.1)	15 (14.6)	1 (1.0)	4 (4.1)	1(1.0)
Observational TF/TA studies															
Gilard et al. 2012 ¹²⁹		2361 TF	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		567 TA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Johansson et al. 2011 ¹²⁰		10 TF	3 (30)	0	2 (20)	NR	2 (20)	0	NR	1 (10)	0	0	NR	0	NR
		30 TA	0	0	0	NR	1 (3.3)	0	NR	1 (3.3)	2 (6.7)	3 (10)	NR	0	NR
		40 SAVR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR
Eltchaninoff et al. 2011 ¹³⁹		161 TF	26 (16)	0	NR	NR	7 (8.7)	0	NR	NR	2 (2.5)	NR	NR	22 (13.7)	NR
		71 TA	2 (2.8)	0	NR	NR	2 (2.8)	0	NR	NR	2 (2.8)	NR	NR	4 (5.6)	NR

† Data extracted from Smith et al. 2011 Supplementary Appendix

Table 31. Clinical complications at 30 days

Study	n (%)	Group (n)	Vascular complications				Neurological events			AKI		Arrhythmia	MI	PPM	Endocarditis
			Major VC	Minor VC	Major Bleeding	Minor Bleeding	Major stroke	Minor stroke	TIA	Stage 3	RRT				
Thomas et al. 2010 ¹²¹		463 TF	55 (12)	51 (11)	24 (5.2)	22 (4.7)	11 (2.4)	0	NR	NR	6 (1.3)	NR	NR	31(6.7)	NR
		575 TA	17 (2.9)	10 (1.7)	32 (5.6)	19 (3.3)	16 (2.6)	0	NR	NR	41 (7.1)	NR	NR	42 (7.3)	NR
Wenaweser et al. 2011 ¹³⁰		157 TF	13(8.3)	11 (7.0)	62 (39.5)	0	6 (3.8)	0	NR	4 (3.1)	NR	NR	0	38 (24.2)	NR
		43 TA	3 (7)	0	26 (60)	0	2 (4.7)	1 (2.3)	NR	5 (11.6)	NR	NR	1 (2.3)	7 (16.3)	NR
Nielsen et al. 2011 ¹⁴⁹		24 TF	1 (4.2)	0	NR	NR	0	0	NR	NR	0	NR	0	1 (4.2)	NR
		76 TA	1 (1.3)	0	NR	NR	1 (1.3)	0	NR	NR	4 (5.2)	NR	3 (3.9)	3 (3.9)	NR
Ewe et al. 2011 ¹⁴¹		45 TF	9 (20)	0	3 (6.7)	0	2 (4.4)	0	NR	NR	NR	NR	NR	2(4.4)	NR
		59 TA	6 (10)	0	9 (15.3)	0	2 (3.4)	0	NR	NR	NR	NR	NR	2 (3.4)	NR
Rodés-Cabau et al. 2010 ¹⁴²		162 TF	22 (13)	0	NR	NR	5 (3.2)	0	NR	NR	3 (1.8)	7.1	2 (1.2)	6 (3.6)	NR
		177 TA	23 (13)	0	NR	NR	3 (1.7)	0	NR	NR	6 (3.4)	9	5 (2.8)	11 (6.2)	NR
Osten et al. 2010 ¹⁴³		16 TF	2 (13)	0	2 (13)	0	1 (6)	1 (6)	0	0	0	NR	0	1 (6)	NR
		30 TA	3 (10)	NR	5 (17)	0	1 (3.3)	0	0	1 (3.3)	NR	NR	0	3 (10)	NR
Bleiziffer et al. 2009 ¹¹⁰		153 TF	24 (16)	0	24 (16)	0	11 (7)	0	0	NR	13 (8)	NR	NR	NR	NR
		50 TA	7 (14)	NR	5 (10)	0	0	0	0	NR	4 (8)	NR	NR	NR	NR

Comparative studies	Outcomes	TAVI (n) VC %		Control (n) VC %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	VC	(179) 16.2	-	(179) 1.1	-	<0.001 ^a
Smith et al. 2011 ¹¹⁶	VC	(244) 14	-	-	(248) 2.9	<0.001 ^b
		-	(104) 3.8	-	(103) 3.9	0.97 ^b
Nuis et al. 2012 ¹¹⁸	VC	(235) 10	-	-	(24) 0	NS
Zierer et al. 2009 ¹¹⁹	VC	-	(21) 10	-	(30) 0	NS
Johansson et al.2011 ¹²⁰	VC	(10) 30	-	-	NR	-
		-	(30) 0	-	NR	-

Abbreviations: MM, medical management; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral

^a P value obtained from Leon et al. 2010

^b P value obtained from Smith et al. 2011, Supplementary Appendix

Comparative studies	Outcomes	TAVI (n) B %		Control (n) B %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	B	(179) 17	-	(179) 3.9	-	<0.001 ^{xxxvii}
Smith et al. 2011 ¹¹⁶	B	(244) 9.5	-	-	(248) 20.2	<0.001 ^{xxxviii}
		-	(104) 8.7	-	(103) 18	0.05 ^{xxxix}
Nuis et al. 2012 ¹¹⁸	B	(235) 9	-	-	(24) 8	1.0
Zierer et al. 2009 ¹¹⁹	B	-	(21) 10	-	(30) 3	0.56
Johansson et al.2011 ¹²⁰	B	(10) 20	-	-	NR	-
		-	(30) 0	-	NR	-

Abbreviations: B, bleeding (major); TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; MM, medical management; SAVR, surgical aortic valve replacement

^{xxxvii} P value obtained from Leon et al. 2010

^{xxxviii} P value obtained from Smith et al. 2011, Supplementary Appendix

Comparative studies	Outcomes	TAVI (n) Stroke %		Control (n) Stroke %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Stroke	(179) 6.7	-	(179) 1.7	-	0.03
Smith et al. 2011 ¹¹⁶	Stroke	(244) 3.7	-	-	(248) 1.7	0.17
		-	(104) 7.0	-	(103) 4.3	0.54
Nuis et al. 2012 ¹¹⁸	Stroke	(235) 5.0	-	-	(24) 8	0.12
Zierer et al. 2009 ¹¹⁹	Stroke	-	(21) 0	-	(30) 3	1.0
Johansson et al.2011 ¹²⁰	Stroke	(10) 20	-	-	NR	-
		-	(30) 3.3	-	NR	-

Abbreviations: MM, medical management; S, stroke; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; SAVR, surgical aortic valve replacement

Comparative studies	Outcomes	TAVI (n) RRT %		Control (n) RRT %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	RRT	(179) 1.1	-	(179) 1.7	-	1.00 ^{xxxix}
Smith et al. 2011 ¹¹⁶	RRT	(244) 2.5	-	-	(248) 2.1	0.77 ^{xl}
		-	(104) 3.9	-	(103) 5.1	0.75 ^s
Nuis et al. 2012 ¹¹⁸	RRT	(235) NR	-	-	(24) NR	-
Zierer et al. 2009 ¹¹⁹	RRT	-	(21) 0	-	(30) 10	0.26
Johansson et al.2011 ¹²⁰	RRT	(10) 0	-	-	NR	-
		-	(30) 6.7	-	NR	-

Abbreviations: MM, medical management; RRT, renal replacement therapy; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TA, transapical; SAVR, surgical aortic valve replacement

^{xxxix} P value obtained from Leon et al. 2010

^{xl} P value obtained from Smith et al. 2011, Supplementary Appendix

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Arrhythmia	(179) 0.6	-	(179) 1.1	-	1.0
Smith et al. 2011 ¹¹⁶	Arrhythmia	(244) 7.4	-	-	(248) 16.5	0.006 [‡]
		-	(104) 11.5	-	(103) 14.6	0.54 [‡]
Nuis et al. 2012 ¹¹⁸	Arrhythmia	(235) 5	-	-	(24) 11	0.27
Zierer et al. 2009 ¹¹⁹	Arrhythmia	-	(21) 0	-	(30) 10	0.26
Johansson et al.2011 ¹²⁰	Arrhythmia	(10) 0	-	-	NR	-
		-	(30) 10	-	NR	-

Abbreviations: TAVI, transcatheter aortic valve implantation; TF, transfemoral; TA, transapical; MM, medical management; SAVR, surgical aortic valve replacement

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	MI	(179) 0	-	(179) 0	-	1.0
Smith et al. 2011 ¹¹⁶	MI	(244) 0	-	-	(248) 0.4	0.32 [§]
		-	(104) 0	-	(103) 1.0	0.31 [§]
Nuis et al. 2012 ¹¹⁸	MI	(235) 1.3	-	-	(24) 4	0.32
Zierer et al. 2009 ¹¹⁹	MI	-	NR	-	NR	-
Johansson et al.2011 ¹²⁰	MI	NR	-	-	NR	-
		-	NR	-	NR	-

Abbreviations: MI, myocardial infarction; MM, medical management; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TA, transapical; SAVR, surgical aortic valve replacement

[‡] P value obtained from Smith et al. 2011, Supplementary Appendix¹¹⁶

[§] P value obtained from Smith et al., 2011, Supplementary Appendix¹¹⁶

Comparative studies	Outcomes	TAVI (n) PPM %		Control (n) PPM %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	PPM	(179) 3.4	-	(179) 5.0	-	0.60 ^{xii}
Smith et al. 2011 ¹¹⁶	PPM	(244) 3.7	-	-	(248) 3.4	0.83 ^s
		-	(104) 3.9	-	(103) 4.1	0.94 ^s
Nuis et al. 2012 ¹¹⁸	PPM	(235) 20.4	-	-	(24) 4	0.07 ^s
Zierer et al. 2009 ¹¹⁹	PPM	-	(21) 0	-	(30) 3	NS ^s
Johansson et al.2011 ¹²⁰	PPM	(10) 0	-	-	0	-
		-	(30) 0	-	0	-

Abbreviations: MM, medical management; PPM, permanent pacemaker; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TA, transapical; SAVR, surgical aortic valve replacement

Comparative studies	Outcomes	TAVI (n) Endocarditis %		Control (n) Endocarditis %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Endocarditis	(179) 0	-	(179) 0	-	-
Smith et al. 2011 ¹¹⁶	Endocarditis	(244) 0	-	-	(248) 0	-
		-	(104) 0	-	(103) 1.0	0.31 ^{xiii}
Nuis et al. 2012 ¹¹⁸	Endocarditis	NR	-	-	NR	-
Zierer et al. 2009 ¹¹⁹	Endocarditis	-	(21) 0	-	(30) 3.3	1.0
Johansson et al.2011 ¹²⁰	Endocarditis	NR	-	-	NR	-
		-	NR	-	NR	-

Abbreviations: MM, medical management; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TA, transapical; SAVR, surgical aortic valve replacement

^{xiii} P value obtained from Smith et al. 2011¹¹⁶ Supplementary Appendix

Table 40. Clinical complications at one year

Study	Group (n)	Vascular complications				Neurological events			AKI			Arrhythmia	MI	PPM	Endocarditis
		Major VC	Minor VC	Major Bleeding	Minor Bleeding	Major stroke	Minor stroke	TIA	Stage 3	RRT					
Experimental TF studies															
Leon et al. 2010 ³⁰	179	30 (17)	28 (15.6)	40 (22.3)	NR	14 (7.8)	4 (2.2)	1 (0.6)	2 (1.1)	3 (1.7)	1 (0.6)	1 (0.6)	8 (4.5)	2 (1.1)	
	179 MM	4 (2.2)	9 (5)	20 (11.2)	NR	7 (3.9)	1 (0.6)	0	5 (2.8)	6 (3.4)	3 (1.7)	1 (0.6)	14 (7.8)	1 (0.6)	
Observational TF studies															
Ussia et al. 2012 ¹²⁶	181	NR	NR	36 (20) ^a	NR	6 (3.4)	NR	NR	NR	NR	NR	NR	NR	NR	
Observational TA studies															
Zierer et al. 2009 ¹¹⁹	21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	
	30 SAVR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1 (3)	
Experimental TF/TA studies															
Smith ¹ et al 2010 ¹¹⁶	248 SAVR	7 (2.9)	2 (0.8)	58 (24.5)	NR	4 (1.7)	1 (0.6)	1 (0.6)	6 (2.8)	12 (5.6)	43 (17.3)	1 (0.4)	9 (3.8)	2 (1.0)	
	244 TF	34 (14)	22 (9)	38 (16.2)	NR	9 (3.8)	2 (0.8)	4 (1.8)	12 (5.4)	12 (5.1)	27 (11.1)	1 (0.5)	13 (5.5)	1 (0.4)	
	104 TA	4 (3.8)	1 (1.3)	11 (11)	NR	8 (8.3)	1 (1.0)	3 (3.7)	0	6 (5.8)	15 (14.4)	0	6 (6.1)	1 (1.2)	
	103 SAVR	5 (5.1)	2 (2.2)	27 (28.5)	NR	4 (4.3)	1 (1.1)	3 (3.7)	2 (2.4)	8 (8.6)	17 (16.5)	1 (1.0)	7 (7.7)	1 (1.0)	
Observational TF/TA studies															
Gilard et al. 2012 ¹²⁹	2361 TF	129 (5.5)	139 (5.9)	65 (2.8)	161 (7)	51 (2.2)	36 (1.5)	NR	NR	NR	NR	20 (0.8)	359 (15)	NR	
	567 TA	11 (1.9)	9 (1.6)	27 (4.8)	54 (9.5)	12 (2.1)	13 (2.3)	NR	NR	NR	NR	10 (1.8)	77 (13.6)	NR	
Thomas et al. 2010 ¹⁴⁰ ; 2011 ¹²¹	463 TF	163 (12.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
	575 TA	12 (2.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	

^a Including life-threatening events

¹ Data reported as Kaplan-Meier estimates at the specific time point obtained from the Supplementary Appendix

Comparative studies	Outcomes	TAVI (n) VC %		Control (n) VC %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	VC	(179) 16.8	-	(179) 2.2	-	<0.001 ^{xliii}
Smith et al. 2011 ¹¹⁶	VC	(244) 14.4	-	-	(248) 2.9	<0.001 ^{xliv}
		-	(104) 3.8	-	(103) 5.1	0.67 ^{xlv}

Abbreviations: MM, medical management; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; SAVR, surgical aortic valve replacement

Comparative studies	Outcomes	TAVI (n) VC %		Control (n) VC %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	VC	(179) 1	-	(179) 2	-	NS
Smith et al. 2011 ¹¹⁶	VC	(244) 0	-	-	(248) 0	NS
		-	(104) 0	-	(103) 1	NS

Abbreviations: MM, medical management; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; SAVR, surgical aortic valve replacement

Comparative studies	Outcomes	TAVI (n) B %		Control (n) B %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	B	(179) 22.3	-	(179) 11.2	-	0.007 ^{xlv}
Smith et al. 2011 ¹¹⁶	B	(244) 16.2	-	-	(248) 24.5	0.02 ^{xlvi}
		-	(104) 11	-	(103) 28.5	0.006 ^{xlvii}

Abbreviations: B, bleeding; MM, medical management; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; SAVR, surgical aortic valve replacement

^{xliii} P value obtained from Leon et al., 2010³⁰

^{xliv} P value obtained from Smith et al., 2011¹¹⁶, Supplementary Appendix

^{xlv} P value obtained from Leon et al., 2010³⁰

^{xlvi} P value obtained from Smith et al., 2011, Supplementary Appendix

Comparative studies	Outcomes	TAVI (n) B %		Control (n) B %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	B	(179) 5.5	-	(179) 11.2	-	0.52
Smith et al. 2011 ¹¹⁶	B	(244) 6.7	-	-	(248) 4.3	0.19
		-	(104) 2.3	-	(103) 10.6	0.03

Comparative studies	Outcomes	TAVI (n) Stroke %		Control (n) Stroke %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Stroke	(179) 10	-	(179) 4.5	-	0.04
Smith et al. 2011 ¹¹⁶	Stroke	(244) 4.6	-	-	(248) 2.3	0.13
		-	(104) 9.3	-	(103) 5.4	0.40

Comparative studies	Outcomes	TAVI (n) Stroke %		Control (n) Stroke %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Stroke	(179) 3.4	-	(179) 2.8	-	NS
Smith et al. 2011 ¹¹⁶	Stroke	(244) 0.8	-	-	(248) 0.4	NS
		-	(104) 2.5	-	(103) 1.0	NS

Comparative studies	Outcomes	TAVI (n) TIA %		Control (n) TIA %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	TIA	(179) 0.6	-	(179) 0.0	-	NS
Smith et al. 2011 ¹¹⁶	TIA	(244) 1.8	-	-	(248) 0.6	NS
		-	(104) 3.7	-	(103) 3.7	NS

Abbreviations: MM, medical management; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; SAVR, surgical aortic valve replacement

Comparative studies	Outcomes	TAVI (n) TIA %		Control (n) TIA %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	TIA	(179) 0.6	-	(179) 0.0	-	NS
Smith et al. 2011 ¹¹⁶	TIA	(244) 0.5	-	-	(248) 0.6	NS
		-	(104) 3.7	-	(103) 2.8	NS

Comparative studies	Outcomes	TAVI (n) RRT %		Control (n) RRT %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	RRT	(179) 1.7	-	(179) 3.4	-	0.50
Smith et al. 2011 ¹¹⁶	RRT	(244) 5.1	-	-	(248) 5.6	0.97
		-	(104) 5.8	-	(103) 8.6	0.57

Comparative studies	Outcomes	TAVI (n) RRT %		Control (n) RRT %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	RRT	(179) 0.6	-	(179) 1.7	-	0.62
Smith et al. 2011 ¹¹⁶	RRT	(244) 2.5	-	-	(248) 2.4	0.8
		-	(104) 1.9	-	(103) 2.9	0.68

Comparative studies	Outcomes	TAVI (n) Arrhythmia %		Control (n) Arrhythmia %		P value
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Arrhythmia	(179) 0.6	-	(179) 1.7	-	0.62 ^{xlvii}
Smith et al. 2011 ¹¹⁶	Arrhythmia	(244) 11.1	-	-	(248) 17.3	0.05
		-	(104) 14.4	-	(103) 16.5	0.70 ^{ee}

^{xlvii} P value obtained from Leon et al., 2010

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		Arrhythmia %		Arrhythmia %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Arrhythmia	(179) 0	-	(179) 0.6	-	NS
Smith et al. 2011 ¹¹⁶	Arrhythmia	(244) 3.7	-	-	(248) 0.8	0.03
		-	(104) 2.9	-	(103) 1.9	NS

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		MI %		MI %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	MI	(179) 0.6	-	(179) 0.6	-	NS
Smith et al. 2011 ¹¹⁶	MI	(244) 0.5	-	-	(248) 0.4	NS
		-	(104) 0.0	-	(103) 1.0	NS

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		MI %		MI %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	MI	(179) 0.6	-	(179) 0.6	-	NS
Smith et al. 2011 ¹¹⁶	MI	(244) 0.5	-	-	(248) 0	NS
		-	(104) 0.0	-	(103) 1.0	NS

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		PPM %		PPM %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	PPM	(179) 4.5	-	(179) 7.8	-	0.27 ^{xlvi}
Smith et al. 2011 ¹¹⁶	PPM	(244) 5.5	-	-	(248) 3.8	0.39 ^{xlvi}
		-	(104) 6.1	-	(103) 7.7	0.68 ^l

^{xlvi} P value obtained from Leon et al., 2010

^{xlvi} P value obtained from Smith et al., 2011, Supplementary Appendix

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		PPM %		PPM %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	PPM	(179) 1.1	-	(179) 2.8	-	0.45
Smith et al. 2011 ¹¹⁶	PPM	(244) 2.8	-	-	(248) 0.4	0.21
		-	(104) 2.2	-	(103) 3.6	0.68

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		Endocarditis %		Endocarditis %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Endocarditis	(179) 1.1	-	(179) 0.6	-	NS
Smith et al. 2011 ¹¹⁶	Endocarditis	(244) 0.4	-	-	(248) 1.0	NS
		-	(104) 1.2	-	(103) 1.0	NS
Zierer et al., 2009	Endocarditis		(21) 0		(30) 3	NS

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		Endocarditis %		Endocarditis %		
		TF	TA	MM	SAVR	
Leon et al. 2010 ³⁰	Endocarditis	(179) 1.1	-	(179) 0.6	-	NS
Smith et al. 2011 ¹¹⁶	Endocarditis	(244) 0.4	-	-	(248) 1.0	NS
		-	(104) 1.2	-	(103) 0.0	NS
Zierer et al., 2009 ¹¹⁹	Endocarditis		(21) 0.0		(30) 3.0	NS

Table 59. Clinical complications at two years

Study	Group (n)	Vascular complications		Bleeding		Neurological events			AKI		Arrhythmia	MI	PPM	Endocarditis
		Major	Minor	Major	Minor	Major stroke	Minor stroke	TIA	Stage 3	RRT				
Experimental TF studies														
Makkar ⁱ et al. 2012 ³¹	179 TF	NR	NR	48 (29)	NR	22 (14)	NR	NR	2 (1.1)	5 (3.2)	NR	2 (1.6)	10 (6.4)	3 (2.3)
	179 MM	NR	NR	25 (20)	NR	8 (5.5)	NR	NR	5 (2.8)	9 (7.6)	NR	2 (2.5)	14 (8.6)	1 (0.8)
Observational TF studies														
Bullesfield ⁱⁱ et al. 2011 ¹²²	72	NR	NR	NR	NR	9 (12.5)	0	3 (4.2)	NR	NR	NR	5 (6.9)	NR	1 (1.4)
Experimental TF/TA studies														
Kodali et al. 2012 ¹¹⁷	248 SAVR	7 (3)	NR	66 (29)	NR	6 (2.9)	0	1 (0.6)	NR	13 (6.2)	NR	2 (1.1)	12 (5.8)	2 (1)
	244 TF	36 (15)	NR	48 (21.5)	NR	13 (5.7)	0	6 (2.8)	NR	14 (6.3)	NR	0	16 (7.2)	3 (1.6)
	104 TA	4 (3.8)	NR	12 (12.4)	NR	11 (12.5)	0	4 (5.8)	NR	6 (5.8)	NR	0	7 (7.1)	1 (1.2)
	103 SAVR	6 (6.1)	NR	29 (31)	NR	8 (9.9)	0	4 (5.4)	NR	8 (8.6)	NR	2 (2.5)	7 (7.7)	1 (1)

ⁱ Data reported as Kaplan-Meier estimates at the specific time point

ⁱⁱ Cardiac reintervention required in 6 patients (8.6%)

Comparative studies	Outcomes	TAVI (n) VC %		Control (n) VC %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	VC	(179) NR	-	(179) NR	-	-
Kodali et al. 2012 ¹¹⁷	VC	(244) 15	-	-	(248) 2.9	<0.001 ⁱⁱⁱ
		-	(104) 3.8	-	(103) 6.1	0.46 ⁱⁱⁱ

Comparative studies	Outcomes	TAVI (n) VC %		Control (n) VC %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	VC	(179) NR	-	(179) NR	-	-
Kodali et al. 2012 ¹¹⁷	VC	(244) 0.6	-	-	(248) 0	NS
		-	(104) 0	-	(103) 0	NS

Comparative studies	Outcomes	TAVI (n) Bleeding %		Control (n) Bleeding %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	Bleeding	(179) 29.0	-	(179) 20	-	0.09 ⁱⁱⁱ
Kodali et al. 2012 ¹¹⁷	Bleeding	(244) 21.5	-	-	(248) 28.9	0.07 ^{iv}
		-	(104) 12.4	-	(103) 31	0.002 ^{iv}

Abbreviations: MM, medical management; TA, transapical; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TF, transfemoral; , surgical aortic valve replacement

ⁱⁱ P value obtained from Kodali et al., 2012, Supplementary Appendix

ⁱⁱⁱ P value obtained from Makkar et al., 2012

^{iv} P value obtained from Kodali et al., 2012, Supplementary Appendix

Comparative studies	Outcomes	TAVI (n) Bleeding %		Control (n) Bleeding %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	Bleeding	(179) 4.7	-	(179) 5.2	-	NS
Kodali et al. 2012 ¹¹⁷	Bleeding	(244) 3.9	-	-	(248) 3.4	NS
		-	(104) 1.4	-	(103) 1.5	NS

Comparative studies	Outcomes	TAVI (n) Stroke %		Control (n) Stroke %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	Stroke	(179) 13.8	-	(179) 5.5	-	0.01 ^{iv}
Kodali et al. 2012 ¹¹⁷	Stroke	(244) 5.7	-	-	(248) 2.9	0.15 ^{lvi}
		-	(104) 12.5	-	(103) 9.9	0.59 ^{lvii}

Comparative studies	Outcomes	TAVI (n) Stroke %		Control (n) Stroke %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	Stroke	(179) 2.6	-	(179) 0	-	NS
Kodali et al. 2012 ¹¹⁷	Stroke	(244) 1.1	-	-	(248) 0.7	NS
		-	(104) 2.9	-	(103) 4.5	NS

Comparative studies	Outcomes	TAVI (n) RRT %		Control (n) RRT %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	RRT	(179) 3.2	-	(179) 7.6	-	NS
Kodali et al. 2012 ¹¹⁷	RRT	(244) 6.3	-	-	(248) 6.2	NS
		-	(104) 5.8	-	(103) 8.6	NS

Abbreviations: S, stroke; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TA, transapical; MM, medical management; SAVR, surgical aortic valve replacement

^{iv} P value obtained from Makkar et al., 2012

^{lvi} P value obtained from Kodali et al., 2012, Supplementary Appendix

Comparative studies	Outcomes	TAVI (n) RRT %		Control (n) RRT %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	RRT	(179) 0.9	-	(179) 2.9	-	NS
Kodali et al. 2012 ¹¹⁷	RRT	(244) 2.2	-	-	(248) 1.1	NS
		-	(104) 0	-	(103) 0	NS

Comparative studies	Outcomes	TAVI (n) MI %		Control (n) MI %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	MI	(179) 1.6	-	(179) 2.5	-	NS
Kodali et al. 2012 ¹¹⁷	MI	(244) 0.0	-	-	(248) 1.1	NS
		-	(104) 0.0	-	(103) 2.5	NS

Comparative studies	Outcomes	TAVI (n) MI %		Control (n) MI %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	MI	(179) 0.8	-	(179) 1.8	-	NS
Kodali et al. 2012 ¹¹⁷	MI	(244) 0.0	-	-	(248) 0.7	NS
		-	(104) 0.0	-	(103) 1.5	NS

Comparative studies	Outcomes	TAVI (n) PPM %		Control (n) PPM %		P value
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	PPM	(179) 1.7	-	(179) 0	-	NS
Kodali et al. 2012 ¹¹⁷	PPM	(244) 1.2	-	-	(248) 2.0	NS
		-	(104) 0	-	(103) 0	NS

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		PPM %		PPM %		
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	PPM	(179) 6.4	-	(179) 8.6	-	NS
Kodali et al. 2012 ¹¹⁷	PPM	(244) 7.2	-	-	(248) 5.8	NS
		-	(104) 7.1	-	(103) 7.7	NS

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		Endocarditis %		Endocarditis %		
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	Endocarditis	(179) 0.9	-	(179) 0	-	NS
Kodali et al. 2012 ¹¹⁷	Endocarditis	(244) 1.2	-	-	(248) 0	NS
		-	(104) 0	-	(103) 0	NS

Comparative studies	Outcomes	TAVI (n)		Control (n)		P value
		Endocarditis %		Endocarditis %		
		TF	TA	MM	SAVR	
Makkar et al. 2012 ³¹	Endocarditis	(179) 2.3	-	(179) 0.8	-	NS
Kodali et al. 2012 ¹¹⁷	Endocarditis	(244) 1.6	-	-	(248) 1.0	NS
		-	(104) 1.2	-	(103) 1.0	NS

Table 74. Clinical complications at three years														
Study n (%)	Group (n)	Vascular complications		Bleeding		Neurological events			AKI		Arrhythmia	MI	PPM	Endocarditis
		Major	Minor	Major	Minor	Major stroke	Minor stroke	TIA	Stage 3	RRT				
Observational TF studies														
Ussia et al. 2011 ¹²⁶	181	NR	NR	37 (29) [§]	NR	7 (3.9)	NR	NR	NR	NR	NR	2 (1.1)	NR	NR

[§] Including life-threatening bleeding

Table 75. Survival data: comparative studies after TAVI			
Study	(n)	1-year survival rate (%)	2-year survival rate (%)
Leon et al. 2010³⁰			
TF	179	69.3	57
MM	179	49.7	32
Smith¹ et al. 2010¹¹⁶			
TAVI	348	75.8	66.1
AVR	351	73.2	65.0
TF	244	77.8	69.1
AVR	248	73.6	65.4
TA	104	71	58.9
AVR	103	72.1	64.3
Nuis¹ 2012 et al.¹¹⁸			
TF	235	69	
AVR	24	80	
MM	99	45	
Johansson¹ et al. 2011¹²⁰			
TF	10	69.5	
TA	30	67	
AVR	40	78.5	
Zierer et al. 2009¹¹⁹			
TA	21	76	
AVR	30	83	

¹ Kaplan-Meier estimates

Table 76. Survival data: case series studies after TAVI

Study (%)	Group (n)	1-year survival rate (%)			2-year survival rate (%)			3-year survival rate (%)		
		Overall	TF	TA	Overall	TF	TA	Overall	TF	TA
TF series										
Ussia ¹ et al. 2012 ¹²⁶	181		76.4			70			65	
Brito ¹ et al. 2012 ¹²⁷	35		76.4			52			52	
Moat ¹ et al. 2011 ¹³⁴	599		81.5		73.7	77.5				
Buellesfeld ¹ et al. 2011 ¹²²	72		72.6			62				
Sinning et al. 2010 ¹³⁶	77		74							
Avanzas ¹ et al. 2010 ¹³⁷	108		82.3							
TA series										
Dewey ¹ et al. 2013 ¹³³	975			77.9						
Walther ¹ et al. 2012 ¹⁴⁵	299			73			68			58
D'Onofrio ¹ et al. 2011 ¹³²	504			81.4			71.5			
Unbehaun ¹ et al. 2011 ¹⁴⁶	300			82.5			64.6			
Ye ¹ et al. 2010 ¹²⁴	71			71.9			66.3			58
TF/TA series										
Gilard ¹ et al. 2012 ¹²⁹	2361/567	76	78.3	67.7						
Thomas ¹ et al. 2011 ¹²¹	463/575	76.1	81.1	72.1						
Nielsen ¹ et al. 2011 ¹⁴⁹	24/76		88	82.7		80	60			
Ewe ¹ et al. 2011 ¹⁴¹	45/59		80	86						
Rodés-Cabau ¹ et al. 2010 ¹⁴²	162/177		75	78		65	64			

¹ Kaplan-Meier estimates

Table 77. Rehospitalisation after TAVI					
Study	Group	Rehospitalisation ^{lviii}			
N (%)	(n)	30 - d	1 - y	2 - y	3 - y
Experimental TF studies					
Leon et al. ³⁰ 2010 and Makkar ^{lix} et al. ³¹ 2012	179 TF	10 (5.6)	40 (22.3)	35%*	
	179 MT	18 (10.1)	79 (44.1)	72.5%*	
Observational TF studies					
Nuis et al. 2012 ¹¹⁸	235 TF	3 (1.3)			
	24 SAVR	0			
	99 MT				
Ussia et al. 2012 ¹²⁶	181		14 (7.6)	NR	34.4%
Hammerer ^{lx} et al. 2011 ¹²⁸	50	5 (10)	7 (14)		
Smith [*] et al. 2011 ¹¹⁶ and Kodali [*] et al. 2012 ¹¹⁷	248 SAVR	3.1%	15.9%	21%	
	244 TF	4.6%	18.5%	23%	
	104 TA	3.9%	17.5%	29%	
	103 SAVR	5.1%	14.7%	24%	

^{lviii} Cardiac related reasons

^{lix} Kaplan-Meier estimates at the specific time point

^{lx} Mean hospital stay, 4 days

* Information obtained from Makkar et al., Supplementary Appendix

* Information obtained from Smith and al. and Kodali et al., Supplementary Appendix

Table 78. Degree of aortic stenosis before and after TAVI

Study	Group (n)	Mean aortic-valve area (cm ²) ±SD				Mean pressure gradient (mmHg) ±SD				Mean left ventricular ejection fraction (LEFV %) ±SD				Paravalvular aortic regurgitation moderate/severe			
		Baseline	30 d	1 y	2 y	Baseline	30 d	1 y	2/3 y	Baseline	30 d	1 y	2/3 y	30 d	1 y	2 y	3 y
Experimental TF Studies																	
Leon et al. 2010, ³⁰ Makkar et al. 2012 ³¹	179 TF	0.6±0.2 ¹	1.5±0.4	1.6±0.5	1.53	44.7±15.4	11.4±7.0	13.2±11.2	9.7 ¹	54±13	58±10.1	57±10.6	59.4 ¹	18 (12)	11 (11)	3 (4.5)	
	179 MM	0.6±0.2 ¹	0.8±0.2	0.7±0.3	NR	43.2±15.4	33.1±12.6	44.3±16.1	NR	51.2±14.3	51.7±13.9	57±10.3	NR	0	0	NR	
Observational TF studies																	
Ussia et al. 2012 ¹²⁶	181	0.6±0.2	1.7	1.8±0.4	1.7 ^a	52.2±18.1	10.3±3.9	10.3±3.1	NR/10±5	51.3±13.1	52.4±11.5	54±10	NR/52±14	27 (15.2)	23 (18)	NR	9 (10) [§]
Brito et al. 2012 ¹²⁷	35	0.7±0.2	NA			51.8±16.3	12.3±5.2 ^b			58±14	58.9±13.5			4 (13)			
Moat et al. 2011 ¹³⁴	599	NR	NR	NR										91 (15.2)			
Zahn et al. 2011 ¹³⁵	697	0.6±0.2				47 ¹ (37-60)	5.4±6.2 ³			52±15.0				16 (2.3)			
Gotzmann et al. 2011 ¹²⁵	150					46.6±13.7				55.8 ± 12.2				25 (17)			
Hammerer et al. 2011 ¹²⁸	50	0.6±0.2	1.8±0.4			55.4±16.3	10.1±5.6			9 (18)	NR			1 (2)			
Danenberg et al. 2010 ¹⁴⁴	55	0.63±0.16	NR			51±13	9±3			58±7	NR			0			
Yong et al. 2012 ¹³¹	119	NR				NR				NR				7 (6)			
Avanzas et al. 2010 ¹³⁷	108	0.63±0.2				55±14.3				NR				NR			
Observational TA studies																	
Walther et al. 2012 ¹⁴⁵	299	NR				NR	8.5±3.5			55±14	55.5±12 ^c			13 (4.3) ^c			
Holzinger et al. 2011 ¹⁴⁷	22	NR				NR	8.2±3.4			NR				0			
Ferrari et al. 2010 ¹⁴⁸	30	0.7±0.16	NR			60.3±20.9	7.7±4.8			52.6±12.8	55.7±10.5			3 (10)			
Ye et al. 2010 ¹²⁴	71	0.6±0.2	1.4±0.3		1.6±0.3	43.6±16.3	10.1±3.9		10.3±6	55.5±12.6	NR		61.2±7	4 (5.2)			
Zierer et al. 2009 ¹¹⁹	21	NR	NR	1.5±0.8	-	NR	NR	9.6±3.7	NA	NR	NR	NR	NA	NR	NR		NA
	30 SAVR	NR	NR	1.7±0.5	-	NR	NR	7.3±3.7	NA	NR	NR	NR	NA	NR	NR		NA

¹ Based on 166 TF and 164 MM

^a Same outcome at 3-year follow-up

[§] Based on 89 patients

^b Reported as post-procedural

^c Data obtained from Kempfer et al. 2011

Table 78. Degree of aortic stenosis before and after TAVI

Study	Group (n)	Mean aortic-valve area (cm ²) ±SD				Mean pressure gradient (mmHg) ±SD				Mean left ventricular ejection fraction (LEFV %) ±SD				Paravalvular aortic regurgitation moderate/severe			
		Baseline	30 d	1 y	2 y	Baseline	30 d	1 y	2/3 y	Baseline	30 d	1 y	2/3 y	30 d	1 y	2 y	3 y
Experimental TF/TA Studies																	
Smith et al. 2011, ¹¹⁶ Kodali et al. 2012 ¹¹⁷	348 TAVI ¹	0.7±0.2	1.7±0.5	1.6±0.5	1.6	42.7±14.5	9.9±4.8	10.2±4.3	12	52.6±13.5	55.5±11.4	57±10.5	NR	35/287 (12.2)	15/222 (6.8)	10/143 (7.0)	
	351 SAVR ¹	0.6±0.2	1.5±0.4	1.4±0.5	1.5	43.5±14.3	10.8±5.0	11.5±5.4	12	53.6±13	56.0±11.4	57±10.3	NR	2/229 (0.9)	3/159 (1.9)	1 (1.0)	
Observational TF/TA Studies																	
Gilard et al. 2012 ¹²⁹	2361 TF	0.7±0.2				48.1±16.5	NR	NR		53.2±14.1	NR	NR	NR	264 ^a (18.6)	NR	NR	NA
	567 TA	0.7±0.2				48.1±16.5	NR	NR		53.2±14.1	NR	NR	NR	30 (5.3)	NR	NR	NA
Eltchaninoff et al. 2011 ¹³⁹	161 TF	0.68±0.16	1.7±0.5 ^b			45.4±15.5	10.5±4.2 ^b			48.6±14.5	55.1±12.9			NR			
	71 TA	0.68±0.17	1.7±0.5 ^b			48±16	10.5±4.2 ^b			54±12	55.1±12.9			NR			
Wenaweser et al. 2011 ¹³⁰	157 TF	0.7±0.2	NR			46±18	NR			51±14	NR			NR			
	43 TA	0.6±0.2	NR			44±15	NR			49±15	NR			NR			
Nielsen et al. 2011 ¹⁴⁹	24 TF	0.6±0.2	1.6±0.4			NR				NR				NR			
	76 TA	0.6±0.2	1.6±0.4			NR				NR				NR			
Ewe et al. 2011 ¹⁴¹	45 TF	0.7±0.2	2.0±0.5			43±19	8±3	NA		55±14	59±13	NA		NR			
	59 TA	0.8±0.2	2.0±0.3			39±12	8±3	NA		52±14	50±13	NA		NR			
Rodes-Cabau et al. 2010 ¹⁴²	162 TF	0.63±0.16	1.55±0.41			48±18	10±4 ¹			55±14				6% ¹			
	177 TA	0.63±0.18	1.55±0.41			44±17	10±4 ¹			56±14				6% ¹			
Osten et al. 2010 ¹⁴³	16 TF	0.6±0.1	1.4±0.2			56±11	12±2	NR		NR	NR			NR			
	30 TA	0.6±0.1	1.6±0.6			52±13	10±3	NR		NR	NR			NR			

¹ Based on 319 TF and 297 SAVR

^a Based on 1418 and 334 patients at risk for the TF and TA group, respectively

^b Data represents global outcome

Table 79. NYHA functional status																
Study (%)	Group (n)	NYHA functional class at baseline			NYHA functional class at 30 Days			NYHA functional class at 1 Year			NYHA functional class at 2 Year			NYHA functional class at 3 Year		
		Class I & II	Class III	Class IV	Class I & II	Class III	Class IV	Class I & II	Class III	Class IV	Class I & II	Class III	Class IV	Class I & II	Class III	Class IV
Experimental TF studies																
Leon et al. 2010 ³⁰ ; Makkar ^{ki} et al. 2012 ³¹	179 TF	8	48	44	63	27	5	75.4	19.7	4.9	83.7	14.7	1.6			
	179 MM	5.4	49	45.6	27	51.3	19	39.3	46.9	13.8	42.8	47.5	9.8			
Observational TF studies																
Ussia et al. 2012 ¹²⁶	181	31	59	10	NR	NR	NR	72	4	0	64	6	0	55	10	0
Brito et al. 2012 ¹²⁷	35	20	54.3	25.7	87	13	0									
Observational TA studies																
Dewey et al. 2013 ¹³³	975	5.8	51	43.1	77	18	4.2	87	8.5	2						
Ye et al. 2010 ¹²⁴	71		86.2 ³					84			75					
Experimental TF/TA Studies																
Smith et al. 2010 ¹¹⁶ ; Kodali et al. 2012 ¹¹⁷	348 TAVI	5.3	41.5	53.2	76.5	19.5	4	84.7	13.9	1.4	84	14.4	1.6			
	351 SAVR	6.0	43.5	50.5	71.5	20.5	8	87	10.3	2.7	85.3	10.8	3.9			
Observational TF/TA Studies																
Gilard et al. 2012 ¹²⁹	2928 TF&TA ^a	24	62	14	81	9.4	1	72	7.5	1						
Eltchaninoff et al. 2011 ¹³⁹	161 TF		76.4		NR ⁵											
	71 TA		75.7		NR ⁵											
Thomas et al. 2011 ¹²¹	463 TF		76.3					78.4								
	575 TA		77.6					69								
Nielsen et al. 2011 ¹⁴⁹	100 TF&TA	20	71	9	87	13	0									
Ewe et al. 2011 ¹⁴¹	45 TF	35.5	53.5	11	NR	NR	NR	58	38	4						
	59 TA	29	58	13	NR	NR	NR	74	26	0						

^{ki} All follow-up intervals are intention-to-treat analysis obtained from Makkar Supplementary Appendix.

⁵ 87.7% when combining both approaches

Table 79. NYHA functional status																
Study	Group	NYHA functional class at baseline			NYHA functional class at 30 Days			NYHA functional class at 1 Year			NYHA functional class at 2 Year			NYHA functional class at 3 Year		
(%)	(n)	Class I & II	Class III	Class IV	Class I & II	Class III	Class IV	Class I & II	Class III	Class IV	Class I & II	Class III	Class IV	Class I & II	Class III	Class IV
Osten et al. 2010 ¹⁴³	16 TF	0	75	25	94	0	0									
	30 TA	0	70	30	93.4	0	0									

Study	Location	Age; (% male)	Enrollment period	Patients at baseline	Patients accessed	Valve	Mean STS score/ Log EuroSCORE at baseline
Gotzmann et al. 2010 ¹⁷⁹	Single centre Germany	79.1 ± 7; 50	Jun 2008 – Jun 2009	50 TF 04 SC	44	CoreValve™ 18 Fr	NR/18.3 ± 12.4
Krane et al. 2010 ¹⁷⁵	Single centre Germany	81 ± 6; 41	Nov 2007 – Dec 2008	73 TF 26 TA	68	SAPIEN™	NR/ 20 (median)
Ussia et al. 2009 ¹⁶⁷	Single centre Italy	81.7 ± 4.7; 43	Apr 2007 – Aug 2008	39 TF	30	CoreValve™ 18 Fr	NR/25.3 ± 8.1
Bekeredjian et al. 2010 ¹⁶⁹	Single centre Germany	86 ± 2.9; 59	Jul 2008 – Jan 2010	87 TF	80	CoreValve™ 18 Fr	18.1 ± 10.2/24 ± 15.1
Gonçalves et al. 2011 ¹⁸⁰	Single centre Spain	81.6 ± 8; 40	Apr 2009 – Apr 2010	49 TF 25 TA	53	SAPIEN™ CoreValve™	NR/ 19.3
Svensson et al. 2008 ¹⁷⁰	Single centre USA	83.7 ± 5.2; 52	Dec 2006 – Feb 2008	40 TA	NR	SAPIEN™	13.4/35.5 ± 15.3
Georgiadou et al. 2011 ¹⁷⁶	Single centre Greece	80.5 ± 5.9; 58	Jun 2008 – Jun 2010	31 TF 5 SC	36	CoreValve™ 18 Fr	NR/29.7 ± 13.7
Gotzmann et al. 2011 ¹⁷¹	Single centre Germany	78 ± 6.6; 49	Jun 2008 – Jun 2009	50 TF 04 SC	51	CoreValve™ 18 Fr	9.3 ± 4.8/19.6 ± 11.3
Krane et al. 2012 ²⁴²	Single centre Germany	80.8 ± 6.8; 37	Nov 2007 – Dec 2009	133 TF 53 TA	186	SAPIEN™ CoreValve™	NR/19.7 ± 12
Lefevre et al. 2011 ¹⁷²	6 European countries ^{lxii}	82.1 ± 5.5; 45	Apr 2007 – Jan 2008	61 TF 69 TA	64 TF ^{lxiii} 43 TA	SAPIEN™	11.6 ± 6.5/30.0 ± 13.7
Ussia et al. 2011 ¹⁶⁸	Single centre Italy	81 ± 4.6; 41	Jun 2007 – Jul 2010	140 TF 3 SC	143	SAPIEN™ XT CoreValve™	7.9 ± 4.0/23.4 ± 14.7
Reynolds et al. 2011 ¹⁶⁵	Multicentre PARTNER B	83±9; 46	May 2007–Mar 2009	179 TF	179	SAPIEN™	11.2 ± 5.8/26.4 ± 17.2 ^{lxiv}

SC, subclavian; TF, transfemoral; TA, transapical

^{lxii} France, The Netherlands, Austria, United Kingdom, Germany and Belgium

^{lxiii} One patient could be assessed by 2 different HRQoL measures

^{lxiv} EuroSCORE data obtained from Leon et al. 2010

Study	Location	Age; (% male)	Enrollment period	Patients at baseline	Patients accessed	Valve	Mean STS score/ Log EuroSCORE at baseline
Reynolds et al. 2012 ¹⁶⁶	Multicentre PARTNER A	83.8±6.8; 60.4 (TF) 82.6±7; 51 (TA)	May 2007–Mar 2009	230 TF 98 TA	165 KCCQ 155 SF-12 160 EQ-5D 65 KCCQ 66 SF-12 61 EQ-5D	SAPIEN™	11.8±3.3 / 29.3±16.5 ^{lxv}
Fairbairn et al. 2012 ¹⁷³	Single centre UK	80±6; 49	May 2008 – May 2010	91 TF 8 SC	99	CoreValve™ 18 Fr	NR/20 ± 13

^{lxv} STS and EuroSCORE data obtained from Smith et al. 2011

Study	Approach / Valve Type	follow-up mean ± SD	HRQoL, instrument (s)	Preoperative	Postoperative
Gotzmann et al. 2010 ¹⁷⁹	TF and TS/ 18-Fr CV	1 m	MLHFQ	MLHFQ 44±19.1	MLHFQ 28±17.5*
Krane et al. 2010 ¹⁷⁵	73 TF 18-Fr CV and 26 TA ES	3 m	SF-36	PCS: 31.2±1.2 MCS: 48.5 ± 1.8	PCS: 38.6 ±1.6* MCS: 47.3 ± 1.7
Ussia GP 2009 ¹⁶⁷	TF 18 Fr CV	5 m	SF-12	SF-12 PCS: 28.5 SF-12 MCS: 37.8	SF-12 PCS: 41.3* F-12 MCS: 48.3*
Bekeredjian et al. 2010 ¹⁶⁹	TF 18 Fr CV	6 m	SF-36	SF -36 PCS: 28.4 ± 10 SF-36 MCS: 37.3 ± 10.8	PCS: 46.8 ± 9.2* MCS: 50.6 ± 10.1
Gonçalves et al. 2011 ¹⁸⁰	21 TF CV, 28 TF and 25 TA ES	6.5 m	MLHFQ	GS: 37.0 ± 14.7 PD: 23.2 ± 9.5 ED: 5.4 ± 4.2	GS: 14.4 ± 10.1* PD: 8.6 ± 5.9* ED: 2.6 ± 3.0*
Svensson et al. 2008 ¹⁷⁰	TA, ES	6 m	SF-12	SF12 PCS: 28.7 ± 6.1 SF-12 MCS: 48.1 ± 11.5	PCS: 35.2 ± 7.4* MCS: 50.4 ± 11.7
Georgiadou et al. 2011 ¹⁷⁶	31 TF 5 TS 18 Fr CV	11.3 ± 4.9 m	SF-36 & SF-12v2	SF-36 PCS: 21.6 SF-36 MCS: 42.9 SF-12v2 PCS: 22 SF-12v2 MCS: 43.3	SF-36 PCS: 46.7* SF-36 MCS: 55.2* SF-12v2 PCS: 48.9* SF-12v2 MCS: 52.2*
Gotzmann et al. 2010 ¹⁷¹	66 TF and 4 TS 18 Fr CV	1 y	MLHFQ	MLHFQ 39.6 ± 19	MLHFQ 26.1 ± 18*
Krane et al. 2012 ²⁴²	TF and TA , CV and ES	1 y	SF-36	PCS: 34.6 ± 2.3 MCS: 48.6 ± 1.2	PCS: 45.6 ± 2.7* MCS: 49.6 ± 1.2
Lefèvre et al. 2011 ¹⁷²	TF and TA, ES	1 y	EQ-5D: 31 TF, 20 TA; KCCQ: 33 TF, 23 TA	EQ-5D: 0.57±0.32 (TF); 0.59 ± 0.30 (TA); KCCQ: 49.9 ± 21.7 (TF); 49.6 ± 22.7 (TA)	EQ-5D: 0.62±0.31 (TF); 0.66 ± 0.43 (TA); KCCQ: 67.9 ±23.7* (TF); 77.1 ± 23.4* (TA)

* statistically significant difference obtained between pre and post-operative, p < 0.001

Table 81. Summary of mid and long-term results of health-related quality of life in patients after TAVI					
Study	Approach / Valve Type	follow-up mean ± SD	HRQoL, instrument (s)	Preoperative	Postoperative
Ussia et al. 2011 ¹⁶⁸	TF 18Fr/ CV and ES XT	1 y	SF-12v2	SF-12 PCS: 28.3 SF-12 MCS: 38.0	SF-12 PCS: 42.4* SF-12 MCS: 48.2*
Reynolds et al. 2011 ¹⁶⁵	TF/ES	1 y	KCCQ and SF-12	KCCQ: 33.6±21.7 SF-12 PCS: 28.2±7.7 SF-12 MCS: 44.5 ±12.2	75.9±27.6* SF-12 PCS: 34.9±11.1* SF-12 MCS: 53.3±10.0*
Reynolds et al. 2012 ¹⁶⁶	TF & TA/ES	1 y	KCCQ SF-12 EQ-5D	KCCQ: 34.1±22.2(TF) SF-12 PCS: 29.7±7.7(TF) SF-12 MCS: 47.0 ±11.5 (TF) EQ-5D: 0.66 ± 0.20 (TF) KCCQ: 34.7±26.9(TA) SF-12 PCS: 29.4±7.4(TA) SF-12 MCS: 46.6 ±11.4 (TA) EQ-5D: 0.67 ± 0.19 (TA)	KCCQ: 38.1 ^a (TF)* SF-12 PCS: 6.3 ^a (TF)* SF-12 MCS: 5.0 ^a (TF) * EQ-5D: 0.09 ^a (TF) * KCCQ: 41.7 ^a (TA)* SF-12 PCS: 7.1 ^a (TA)* SF-12 MCS: 3.6 ^a (TA); p=0.04 EQ-5D: 0.06 (TA); p=0.03
Fairbain et al. 2012 ¹⁷³	TF/18 Fr CV	1 y	SF-12v2 & EQ-5D	SF-12 PCS: 29.5 ± 9 SF-12 MCS: 45.4 ± 12 EQ-5D: 0.54 ± 0.3	SF-12 PCS: 34.4 ± 10* SF-12 MCS: 46.9 ± 11 EQ-5D: 0.65 ± 0.3*

^a values denote mean difference versus baseline

* statistically significant difference obtained between pre and post-operative, p<0.001

Study	Location	Data source/ Study design/ Enrollment period	Study size/ approach/ Type of valve/ follow up	Aim of assessment/ Prior knowledge of the outcome	Methods/numbe r of surgeons involved	Type of outcome used to assess the learning curve	Main findings
Alli et al. 2012 ¹⁸³	Single centre USA	Retrospective analysis of the PARTNER TRIAL RCT Nov 2008 – May 2011	44 TF SAPIEN™XT 30 days	To assess physicians performing the TF route/NR	Two grps of 22 pts each, from PARTNER A and B divided in 3 tertiles/Unclear	Intraoperative continuous measures defined as procedure times, radiation exposure and contrast administration with a significant decrease	Significant decrease in cutdown-to-sheath and cutdown-to-valvuloplasty times (from medians of 42.5 to 43.1 to 19.0 min and 61.5 to 51.7 to 42.5 min, $p = 0.002$ and $p < 0.001$ respectively) Valvuloplasty-to-valve deployment time decreased from 12.0 to 11.6 and 7.0 min from tertiles 1 to 3, respectively, $p < 0.001$, and fluoroscopy times, from 26.1 to 17.2 and 14.3 min, respectively, from tertiles 1 to 3, $p < 0.001$. In median contrast, authors conclude it takes about 30 interventions to reach proficiency, but recommend further studies to confirm these findings due to a limited sample size.
Kempfer et al. 2011 ¹⁶²	Single centre Germany	Retrospective Case series Feb 2006 – Jan 2010	299 TA SAPIEN™ 1 year	To assess a learning experience over 4-years using a multivariate logistic regression to ID independent mortality risk factors/NR	Pts divided in 2 halves: Early Experience (1 to 150) vs. Recent Experience grp (151 to 299)/Unclear	Postoperative dichotomous variables such as death and survival	Reported a reduction in 1 month mortality rates from 11% in the first 150 pts Improvement in 1-year mortality from 30.7% to 21.5% between the two grps ($p = 0.047$)

Study	Location	Data source/ Study design/ Enrollment period	Study size/ approach/ Type of valve/ follow up	Aim of assessment/ Prior knowledge of the outcome	Methods/numbe r of surgeons involved	Type of outcome used to assess the learning curve	Main findings
Gurvitch et al. 2011 ¹⁸¹	Single centre Canada	Prospective Case series NR	169 TF 101 TA SAPIEN 1 month	To evaluate the impact of the LC on patient outcomes	2 equal TF groups: first vs. second half 2 equal TA groups: first vs. second half/ NR	Post-operative dichotomous outcomes	TF: Observed improvement in the 30-day mortality from 10.7% (FH) to 4.7% (SH). TA: Also observed improvement in the 30-day mortality from 17.6% (FH) to 7.8% (SH) Failure to deliver the transcatheter valve was only noted in the TF approach (FH 7.1 vs. SH 0%, p = 0.01)
Webb et al. 2007 ¹⁸²	Single centre, Canada	NR Case series NR	50 TF	To evaluate the impact of the LC on patient outcomes	2 equal TF groups: first half (25) vs. second half (25)	Post-operative dichotomous outcomes	Procedural success improvement from 76% (1st) to 96% (2nd); Intraprocedural mortality from 4% to 0%; valve malposition decrease from 8% to 0%
Wendler et al. 2010 ¹⁵⁵	Multicentre SOURCE Registry Europe	Retrospective Case series Jan 2008 – Jan 2009 Feb 2009 - Jan 2010	1394 TA SAPIEN 1 month	To analyze the learning curve for TAVI over the first 2 years after commercialization	Two grps of patients: G1-575 vs G2-819	Post-operative dichotomous outcomes	30-day mortality (G-1: 10.8%, G-2:10.7%; p = NS) Aortic regurgitation >2+ (G-1: 4.52%, G-2:2.1%; p < 0.05) Conversion rate to SAVR ((G-1: 3.7%, G-2:1.5%; p < 0.05)

Abbreviations: FH, first half; grp, group; min, minutes; LC, learning curve; NR, not reported; NS, not specified; pt, patient; SAVR, surgical aortic valve replacement; SH, second half; TA, transapical; TF, transfemoral; TAVI, transcatheter aortic valve implantation

Table 83. Mean pooled outcomes in TF vs TA groups

Outcomes (studies, n)	Intervention		p Value	Fvs TF	Fvs TA
	TF Mean (SD)	TA Mean (SD)			
Characteristics at baseline					
Patients age (32)	82 (7.1)	81 (7.2)	< 0.001	X	-
STS score (20)	9.4 (11)	11.5 (11.3)	< 0.001	-	X
EuroSCORE (29)	27.9 (16.3)	22.6 (14.7)	< 0.001	X	-
Operative outcomes					
Procedural time in minutes (12)	77.1 (41)	116.3 (53)	-	X	-
Length of ICU/CCU in days (3)	NR	2.5 (2.7)	-	-	-
Length of hospital stay in days (5)	9.1 (8.1)	10.7 (8.1)	< 0.001	X	-
Echocardiographic findings					
	TAVI			Fvs B	Fvs A
Aortic valve area (10)	0.65 (0.2)	1.6 (0.5)	< 0.001		X

Abbreviations: SD, standard deviation; Fvs, favours; B, before; A, after

Table 84. Complication/outcome rates in TF vs TA groups from case series studies

Outcomes (Studies, n)	Patient-reported outcome (n)/ pooled total (N)			Fvs TF	Fvs TA
	TF n/N	TA n/N	p Value		
Gender (32)	5455/10411	4956/10411	<0.001 ^{lxvi}	NA	NA
Procedural success (19)	4820/4995	2316/2631	NS	-	-
Valve-in-valve (18)	86/4601	70/2596	0.02	X	
Conversion to SAVR (25)	39/5491	45/2656	<0.001	X	
Mortality					
At day 3					
Overall (21)	37/1573	20/667	NS	-	-
Vascular complications (17)	21/921	2/419	0.02		X
At 30 days					
All-cause (34)	553/6466	385/4034	0.08	X	
Cardiac (27)	242/4234	141/2236	NS	-	-
Vascular complication (21)	27/1323	9/1223	<0.01		X
Cardiac/MOF ^{lxvii} (19)	27/1120	39/1223	NS	-	-
Valve related (21)	16/1350	4/1223	0.01		X
Non-cardiac (26)	114/4157	69/2236	NS	-	-
Stroke (21)	14/1170	7/1472	0.04		X
Sepsis (21)	7/1170	12/1515	NS	-	-
Respiratory causes (21)	9/1170	10/1472	NS	-	-
At 1 year					
All-cause (4)	179/681	30/104	NS	-	-
Cardiac (4)	81/681	19/104	NS	-	-
Non-cardiac (4)	100/681	11/104	NS	-	-
At 2 years					
All-cause (3)	184/495	42/104	NS	-	-
Cardiac (3)	112/495	24/104	NS	-	-
Non-cardiac (3)	72/495	18/104	NS	-	-
Complications					
At day 3					
Vascular complications (23)	262/2580	101/2066	<0.01		X
Major bleeding (12)	101/1544	62/1509	<0.01		X
Major and minor stroke (15)	32/1657	4/625	0.02		X
MI (14)	34/1958	5/921	<0.01	X	
At 30 days					
Vascular complications(27)	444/3393	120/2042	<0.0001		X
Major bleeding(22)	397/2344	70/1163	<0.0001		X
Neurological events					
Stroke (major/minor) (30)	153/3909	59/3437	<0.0001		X
TIA(11)	8/1451	0/184	NS		
AKI stage 3(17)	47/1680	18/444	NS		

^{lxvi} Favours males

^{lxvii} MOF, multi organ failure

Table 84. Complication/outcome rates in TF vs TA groups from case series studies

Outcomes (Studies, n)	Patient-reported outcome (n)/ pooled total (N)			Fvs TF	Fvs TA
	TF n/N	TA n/N	p Value		
RRT(20)	49/1994	145/1989	X		
Arrhythmia (8)	43/1582	31/332	<0.0001		X
At 30 days - Continued					
MI (19)	49/3083	17/964	NS	-	-
PPM (28)	655/3276	217/2979	<0.0001		X
PPM with ES valve (16)	234/2867	217/2979	NS	-	-
Endocarditis (7)	0/566	5/724	NS	-	-
At 1 year					
Vascular complications(4)	222/3247	27/1246	0.0001		X
Major bleeding(4)	182/2965	39/671	NS	-	-
Stroke (major/minor) - (4)	123/2965	35/671	NS	-	-

Abbreviations: TF, transfemoral; TA, transapical; Fvs., favours ; SAVR, surgical aortic valve replacement; TIA, transient ischemic attack; AKI, acute kidney injury; RRT, renal replacement therapy

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