NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis

Aortic stenosis occurs when the aortic valve becomes narrowed. This reduces the flow of blood out of the heart. Catheter insertion of a new aortic valve (a procedure called 'transcatheter aortic valve implantation' or TAVI for short) may be an alternative to surgical valve replacement in patients for whom conventional aortic valve replacement by open heart surgery is not suitable, or who are at high risk of serious complications. The aim is to insert the new valve through a thin tube, usually into a large blood vessel at the top of the leg, and to place it over the existing faulty valve.

Introduction

The Birmingham & Brunel Consortium External Assessment Centre (B&BC) and National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a systematic review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

In April 2011 the National Institute for Health and Care Excellence (NICE) prepared a rapid overview to inform members of the Interventional Procedures Advisory Committee (IPAC) in order to make recommendations about the safety and efficacy of transcatheter aortic valve implantation (TAVI) for patients with aortic stenosis. Based on the rapid overview of the medical literature and specialist opinion, NICE issued interventional procedure guidance (IPG) 421 on the safety and efficacy of TAVI for patients with aortic stenosis [NICE 2012], which replaces the previous guidance on the technology, NICE interventional procedure guidance 266, published in June 2008.

NICE commissioned the Birmingham & Brunel Consortium External Assessment Centre (B&BC) to undertake a systematic review of the literature [(1)]. Since the publication of NICE IPG 421 there has been some new evidence on this technology published in the medical literature. Thus, NICE commissioned the B&BC to identify and summarise evidence from the current best 7 studies from the literature, to inform the IPAC of a potential update of NICE IPG 421.

Date prepared

This IP overview was prepared in January 2017

Procedure name

Transcatheter aortic valve implantation for aortic stenosis

Specialist societies

- Society of Cardiothoracic Surgery of Great Britain and Ireland
- British Cardiovascular Intervention Society
- British Society of Echocardiography

Description

Indications and current treatment

Aortic stenosis causes impaired outflow of blood from the heart and is usually progressive. The increased cardiac workload leads to left ventricular hypertrophy and heart failure. Symptoms of aortic stenosis typically include shortness of breath and chest pain on exertion.
Surgical aortic valve replacement (SAVR) with an artificial (biological or mechanical) prosthesis is the conventional treatment for patients with severe symptomatic aortic stenosis who are well enough for surgery. Optimal medical care has traditionally been the only option for those whose condition is unsuitable for surgery. Aortic balloon valvuloplasty is occasionally used. SAVR may be unsuitable for patients because of medical comorbidities or technical considerations (for example, if the patient has a calcified aorta or scarring from previous cardiac surgery), which mean that the risks of surgical aortic valve replacement outweigh the potential benefits. Patients for whom SAVR is suitable range from those considered to be high risk (for example, as defined in the PARTNER 1A trial) to those for whom the benefits of surgery clearly outweigh the risks of surgery.

What the procedure involves

Transcatheter aortic valve implantation (TAVI) aims to provide a less invasive alternative to open cardiac surgery for treating aortic stenosis, avoiding the need for cardiopulmonary bypass.

The procedure is carried out under general anaesthesia or using local anaesthesia with sedation. Imaging guidance, including fluoroscopy, angiography and transoesophageal echocardiography is required. Prophylactic antibiotics and anticoagulation medication are administered before and during the procedure. Temporary peripheral extracorporeal circulatory support (usually via the femoral vessels) is sometimes used.

The procedure implants a bioprosthetic aortic valve at the site of the native aortic valve. Access to the aortic valve can be achieved transluminally, with entry to the circulation usually achieved via the femoral or other large artery or vein (sometimes known as a percutaneous, or endovascular approach); or surgically, with access to the aortic valve via apical puncture of the left ventricle using a minithoractomy approach (transapical, or transventricular approach). In the transluminal approach, when the femoral or other large artery is used, surgical exposure and closure may be needed. The choice of how catheter access to the aortic valve is achieved may depend on the existence of factors that make passage through the circulation difficult such as peripheral vascular disease.

A balloon catheter is advanced over a guidewire placed across the aortic valve. The existing aortic valve is dilated and the new prosthetic valve is manipulated into position and placed over the existing aortic valve. To provide a stable platform for aortic valve implantation, rapid right ventricular pacing is used to temporarily interrupt blood flow through the native aortic valve. The new valve is mounted on a metal stent which is either self-expanding or expanded using inflation of a large balloon on which the stented valve has been crimped. Positioning the new valve leads to obliteration of the native aortic valve. The delivery catheter is removed after successful valve placement.

Different devices are available for this procedure. Some may contain material derived from animal sources.

Clinical assessment tools

Clinical assessment of severity of aortic stenosis:

- New York Heart Association (NYHA) heart failure classification: this is used to classify the severity of breathlessness; from class I, in which the patient has no limitation in daily physical activity, to class IV, in which the patient is breathless at rest.
- Haemodynamic assessment (usually by echocardiography and Doppler):
  - Aortic valve area (cm^2) or aortic valve area index (relative to body surface area; cm^2/m^2). An aortic valve area of less than 0.6 cm^2/m^2 indicates severe aortic stenosis.
  - Transaortic gradient (mmHg). Peak transaortic valve gradient of more than 64 mmHg and mean transaortic valve gradient of more than 40 mmHg indicates severe aortic stenosis.

The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) measures patient risk at the time of surgery using a logistic-regression equation on a 0 to 100% scale (higher scores indicating greater risk; a score higher than 20% indicates very high surgical risk).

Literature review

The systematic review undertaken to produce this overview aimed to address the following research questions:

1. What is the current evidence base for the efficacy and safety of TAVI?
2. What is the comparative safety and effectiveness of TAVI compared with other treatments for aortic stenosis (including but not necessarily limited to SAVR and conservative management)?

The evidence will be presented for the following 3 distinct groups of patients with aortic stenosis (as identified in NICE IPG 421):

- for whom SAVR is considered unsuitable
- for whom SAVR is considered suitable but poses a high risk
- for whom SAVR is considered suitable and for whom it does not pose a high risk.

Table 1 below lists the details of inclusion and exclusion criteria for the decision problem in terms of relevant population, intervention, comparator, safety and efficacy outcome, and study types.

Table 1: Inclusion and exclusion criteria

Characteristic	Criteria
Publication type	For evidence on efficacy: published randomised or non-randomised controlled trials, comparative cohort studies, and case-control studies or systematic reviews of such studies will be included. For evidence on safety (including long term patient survival, and short and long term valve function/durability): in addition to the types of studies above-mentioned, before-and-after studies, descriptive cohort studies and case series with long-term follow-up and large sample size will only be included if they report longer follow-up outcomes than those reported in comparative studies or systematic reviews. Minimum duration of follow-up and minimum number of patients will be determined following assessment of the available studies. Case reports and conference abstracts will only be included if they report important and rare safety events that are not reported in the types of aforementioned studies. Narrative review, editorial, laboratory study, animal study and unpublished material will be excluded.
Patient	Patients of any age with aortic stenosis (patients with aortic bioprosthetic valve dysfunction will be excluded).
Intervention	TAVI, including procedures performed using different types of devices and different implantation techniques. Evidence will be included on all substantial modifications directly related to the procedure such as newer devices used, new/modified approaches and delivery systems/equipment. With regarding to modifications of the TAVI procedure, the review will focus on factors that are directly related to TAVI valves, delivery systems/equipment (e.g. catheter), and implantation technique including delivery route and positioning. Studies looking at the impact of ancillary variations of the TAVI procedure (such as types of anaesthetic, types of imagine examination/guidance, learning curve, etc.) rather than the above mentioned will be excluded. Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction will be excluded from this systematic review as separate NICE guidance on this procedure has been published. TAVI with balloon aortic valvuloplasty will be included. TAVI in combination with any other surgical cardiac procedure will be excluded.
Comparator	Standard therapies (conservative management with optimal medical care and/or aortic balloon valvuloplasty; SAVR), or no intervention. Surgical replacement combined with any other surgical cardiac procedure will be excluded.

Outcome	Clinical efficacy outcomes including: technically successful valve implantation, reduction of symptoms, severity of aortic valve stenosis, occurrence regurgitation, ejection fraction/cardiac index (echocardiography or angiography), cardiac function/NYHA heart failure class and quality of life. Safety outcomes of any complications and adverse events, including long term patient survival, and short and long term valve function/durability. Surrogate outcomes (such as platelet volume or other biomarkers as the indicator of any clinical outcomes) will be excluded.
Language	Non-English-language articles will be excluded.

Abbreviation: TAVI, transcatheter aortic valve implantation; NYHA, New York Heart Association (Functional Classification); SAVR, surgical aortic valve replacement

List of studies included in the IP overview

This IP overview is based on 16,638 patients from 5 randomised controlled trials (RCTs) and 2 systematic reviews. The RCTs have generated a number of peer reviewed papers reporting different follow-up points for outcomes and sub-analyses for different patient groups (which are reported in the systematic review undertaken for this IP overview [(1)].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction tables (tables 2 to 8) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on transcatheter aortic valve implantation for aortic stenosis

Study 1:Kapadia SR (2015) [(2)]

Kapadia SR 2015 paper reports 5 year follow-up data. This table also draws on information presented in earlier papers by Leon MB (2010) [(3)] Reynolds MR (2011) [(4)], Makkar RR (2012) [(5)], Kapadia SR (2014) [(6)].

Details

Study type	**Randomised control multicentre trial** (PARTNER 1B)
Country	US, Canada and Germany
Recruitment period	2007 to 2009
Study population and number	n=**358** inoperable patients **(TAVI n=179 versus standard therapy n=179)**
Age and sex	**Mean age 83.2 years** (SD 7.1); 46.4% (183/358) females
Patient selection criteria	Inclusion Criteria • Senile degenerative aortic valve stenosis; symptomatic due to aortic valve stenosis as demonstrated by NYHA Functional Class ≥ II. • The probability of death or serious, irreversible morbidity exceeded the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity exceeded 50%. Exclusion Criteria • Life expectancy < 12 months due to non-cardiac co-morbid conditions. • Recent acute myocardial infarction (≤ 1 month) or cerebrovascular accident or transient ischemic attack (within 6 months) or renal insufficiency and/or end stage renal disease requiring chronic dialysis. • Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified. • Mixed aortic valve disease; untreated clinically significant coronary artery disease requiring revascularization; any therapeutic invasive cardiac procedure performed within 30 days ; pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, or severe mitral regurgitation; native aortic annulus size < 18mm or > 25mm • Blood dyscrasias; hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices. • Hypertrophic cardiomyopathy with or without obstruction; severe ventricular dysfunction with LVEF < 20%; echocardiographic evidence of intracardiac mass, thrombus or vegetation. • Active peptic ulcer or upper gastro-intestinal bleeding within the prior 3 months. • A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine or clopidogrel or sensitivity to contrast media, which cannot be adequately pre-medicated. • Significant abdominal or thoracic aorta disease, including), aortic arch atheroma, narrowing of the abdominal aorta or severe “unfolding” and tortuosity of the thoracic aorta • Vessel characteristics that would preclude safe placement of introducer sheath • Active bacterial endocarditis or other active infections.
Technique	TAVI under general anaesthesia (transfemoral route) versus standard treatment (including balloon aortic valvuloplasty in 150). A standard balloon aortic valvuloplasty was performed, followed by transfemoral insertion of either a 22- or 24-French sheath, depending on the selected size of the valve (23 mm or 26 mm). Edwards SAPIEN heart-valve system (Edwards Lifesciences).
Follow-up	**5 years** (30 days, 6 months, 1 year, 2 and 5 years)
Conflict of interest/ source of funding	Sponsored by Edwards Lifesciences. The study authors declared receiving consulting and lecture fees from a number of different medical device manufacturers.

Analysis

Follow-up issues:

- After all patients completed 1 year of follow-up, those in the standard treatment group could crossover to the TAVI group. Data from patients in the standard treatment group who crossed over to TAVR were censored at the time of crossover.
- 6 patients in standard treatment group withdrew.

Study design issues:

- 21 centres (17 in the USA)
- The 358 patients represent results from cohort B; results from cohort A (those at high risk but candidates for surgery) are not yet published.
- 2 surgeons decided if a patient was considered suitable.
- Computer-generated block randomisation.
- Time between randomisation and treatment was a median of 6 days for TAVI; it was within 30 days in 63.7% (114) of patients in TAVI group and 20.1% (36) of patients in the comparator group.
- Serious events adjudicated by independent committee.
- All events reviewed once as blinded review and then un-blinded.
- Cross-over was not permitted.
- Authors calculated that 350 patients gave 85% power assuming 1-year mortality would be 25% in TAVI group compared with 37.5% in comparator.

The study was assessed to be at risk of having performance bias as there was no blinding of participants and personnel. The risk of selection and reporting biases is unclear.

Study population issues:

- 2 patients randomised to TAVI died before the procedure.
- Patients treated with TAVI had a significantly lower Logistic EuroSCORE (26.4±7.2 versus 30.4±19.1, p=0.04), less presence of atrial fibrillation (p=0.04) and higher rate of extensively calcified aorta (p=0.05).
- Even though patients included were unsuitable for surgery, 12 patients had aortic valve replacement (AVR), 5 had a conduit from left ventricle to descending aorta and AVR, and 4 had TAVI at a non-participating site outside the US.

Other issues: The authors acknowledge that not collecting quality of life data after year 1 limited their ability to assess the benefit of TAVI for inoperable patients.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **358 (179 TAVI vs 179 standard therapy including balloon aortic valvuloplasty in 150)**

Of those treated with TAVI, 4 did not receive a valve because of difficulties with transfemoral access (n=2) or an intra-procedural annulus that was too large (n=2).

Death (Kaplan-Meier analysis)

	TAVI	Standard therapy	Hazard ratio	P valve
1 year (5)				
Death (any cause)[a,]	30.7%	50.7%	0.55 (95% CI 0.40 to 0.74)	< 0.001
Death (cardiovascular cause)[b]	20.5%	44.6%	0.39 (95% CI 0.27 to 0.56)	< 0.001
2 years (5)				
Death (any cause)[c]	43.3%	68.0%	0.56 (95% CI 0.43to 0.73)	<0.001
Death (cardiovascular cause)[d]	31.0%	62.4%	0.44 (95% CI 0.32 to0.60)	<0.001
3 years (6)				
Death (any cause)	54.1%	80.9%	0.53 (95%CI 0.41 to 0.68)	<0.0001
Death (cardiovascular cause)	41.4%	74.5%	0.41 (95%CI 0.30 to 0.56)	<0.0001
5 years (2)				
Mortality (all cause)	71.8%	93.6%	0.50 (95% CI 0.39 to0.65),	<0.0001
Mortality (cardiac related)	57.5%	85.9%	0.41 (95%CI 0.31 to 0.55),	<0.0001

Deaths from unknown causes were assumed to be from cardiovascular causes,

[a] actual observed values were 30.7% (55/179) and 49.7% (89/179)

[b] actual observed values were 19.6% (35/179) and 41.9% (75/179)

[c] actual observed values were 43.0% (77/179) and 65.4% (117/179)

[d] actual observed values were 20.5% (35/179) and 44.6% (75/179)

Requirement for further treatment at 30 days and 1 year [(3)]

	TAVI	Standard Therapy	P valve
30 days			
Balloon aortic valvuloplasty	0.6% (1/179)[a]	1.1% (2/179)	1.00

Safety

30-day complications[(3)]

	TAVI	Standard therapy	p value
Death (any cause)	5.0% (9/179)	2.8% (5/179)	0.41
Death (cardiovascular cause)	4.5% (8/179)	1.7% (3/179)	0.22
Repeat hospitalisation related to condition/valve	5.6% (10/179)	10.1% (18/179)	0.17
All strokes	6.7% (12/179)	1.7% (3/179)	0.03
Minor stroke	1.7% (3/179)	0.6% (1/179)	0.62
Major stroke	5.0% (9/179)	1.1% (2/179)	0.06
Vascular complications (considered major)	30.7% (55/179) [16.2% (29/179)]	5.0% (9/179) [1.1% (2/179)]	< 0.001 [< 0.001]
Acute kidney injury requiring renal replacement therapy	1.1% (2/179)	1.7% (3/179)	1.00
Major bleeding	16.8% (30/179)	3.9% (7/179)	<0.001
New atrial fibrillation	0.6% (1/179)	1.1% (2/179)	1.00
New pacemaker	3.4% (6/179)	5.0% (9/179)	0.60
Moderate or severe paravalvular AR	11.8%18/153)		

Moderate or severe aortic regurgitation [(3)]

		TAVI	Standard therapy
Baseline	All	20% (35/173)	13% (23/174)
	Trans-valvular	20% (35/173)	13 % (23/147)
	Para-valvular	0	0
30 days	All	15% (23/153)	17% (21/125)
	Trans-valvular	1 % (2/153)	17% (21/125)
	Para-valvular	12% (18/153)	0

Repeat TAVI[b]	1.7% (3/179)	n/a	
- AVR	0	1.7% (3/179)	0.25
1 year			
Balloon aortic valvuloplasty	0.6% (1/179)	36.9% (66/179)	< 0.001
Repeat TAVI	1.7% (3/179)	n/a	
AVR	1.1% (2/179)	9.5% (17/179)	< 0.001

[a] this was caused by failed access (patient first had balloon aortic valvuloplasty, then AVR, [b] within 24 hours after index procedure to treat clinically significant aortic regurgitation (paravalvular in 2 and transvalvular in 1 patient).

Functional outcome
NYHA class

Asymptomatic or mild (NYHA class I or II)	TAVI	Standard therapy	p value
Baseline(3) (Leon, 2010)	7.8% (14/179)	6.1% (11/179)	0.605
At 1 year(3) (Leon, 2010)	74.8% (88/118)	42.0% (33/79)	< 0.001
2 years(5) (Makkar, 2012)	83% (79/95)	42% (17/40)	<0.0001
3 years(6) (Kapadia, 2014)	70% (49/70)	50% (7/14)	0.245
5 years (Kapadia, 2015)	85.7% (42/49)	60% (3/5)	0.531

(of surviving patients; exact patient numbers not reported, calculated by analyst).

6-minute walk test

This test could only be performed in a subgroup of patients because of coexisting conditions preventing patients from taking part. At 1 year, paired analysis of the distance covered during the test showed a significant improvement after TAVI (p = 0.002) but not after standard therapy (p = 0.67) (number of patients who participated and exact distance not reported in main study).

Haemodynamic performance (on echocardiography) [3, 4]

	TAVI	Standard therapy
LVEF (%)*		
- baseline	53.9 ± 13.1	51.2 ± 14.3
- 30 days	57.9 ±10.1	51.7 ±13.9
- 1 year	57.2 ± 10.6	56.9 ± 10.3
Mean aortic valve area (cm^2)*		
- baseline	0.6 ± 0.2	0.6 ± 0.2
- 30 days	1.5 ± 0.4	0.2 ± 0.2
- 1 year	1.6 ± 0.5	0.7 ± 0.3
- 2 years (median, IQR)	1.53 (1.28-1.85)	

1 year	All	15% (15/98)	17% (9/52)
	Trans-valvular	4% (4/98)	17% (9/52)
	Para-valvular	11% (11/98)	0

Complications to 1 year [3]

	TAVI	Standard therapy	p value
Repeat hospitalisation related to condition/valve	22.3% (40/179)	44.1% (79/179)	< 0.001
All Stroke or TIA:	10.6% (19/179)	4.5% (8/179)	0.04
TIA	0.6% (1/179)	0	1.00
Minor stroke	2.2% (4/179)	0.6% (1/179)	0.37
Major stroke	7.8% (14/179)	3.9% (7/179)	0.18
Myocardial infarction	0.6% (1/179)	0.6% (1/179)	1.00
Major vascular complications	32.4% (58/179) 16.8% (30/179)	7.3% (13/179)/ 2.2% (4/179)	< 0.001 < 0.001
Acute kidney injury requiring renal replacement therapy	1.7% (3/179)	3.4% (6/179)	0.50
Major bleeding	22.3% (40/179)	11.2%(20/179)	0.007
Endocarditis	1.1% (2/179)	0.6% (1/179)	0.31
New atrial fibrillation	0.6% (1/179)	1.7% (3/179)	0.62
New pacemaker	4.5% (8/179)	7.8% (14/179)	0.27

2 years [5]

	TAVI	Standard therapy	p value
Repeat hospitalisation(a)	35%(53/179)	72.5%(95/179)	HR (95%CI 0.30 to 0.58)
Stroke(a)	13.8% (22/179)	5.5%(8/179)	0.01
Myocardial infarction(a)	1.6%(2/179)	2.5%(2/179)	0.69
Acute kidney injury requiring renal replacement therapy(a)	3.2%(5/179)	7.6% (9/179)	0.15
Major bleeding(a)	48 (28.9%)	25 (20.1%)	0.04
Endocarditis(a)	3 (2.3%)	1 (0.8%)	0.32
New pacemaker[(a)]	10 (6.4%)	14 (8.6%)	0.47

Mean pressure gradient (mm Hg)		
- baseline	44.7 ± 15.4	43.2 ± 15.4
- 30 days	11.4 ± 7.0	33.1 ± 12.6
- 1 year	13.2 ± 11.2	44.3 ± 16.1
- 2 years (median, IQR)	9.7 (7.7-13.3)	

*p < 0.001 for difference from baseline to 30 days (improvement was maintained at 1 year but significance level not given)

Quality of life [4]

	Between-Group Differences (TAVI-Control)	95% CI	P value
KCCQ quality of life			
1 month	14.8	8.6 to 21.0	<0.001
6 months	24.2	17.4 to 31.0	<0.001
12 months	30.5	22.3 to 38.7	<0.001
SF-12 Physical			
1 month	4.5	2.5 to 6.6	<0.001
6 months	5.5	3.0 to 7.9	<0.001
12 months	5.7	2.8 to 8.5	<0.001
SF-12 mental			
1 month	0.6	-1.6 to 2.6	0.61
6 months	3.2	1.1 to 5.3	0.003
12 months	6.4	3.5 to 9.4	<0.001

Adjusted effect of TAVI vs standard therapy according to random effect growth curve models. Positive values indicate better status with TAVI

Moderate to severe paravalvular aotic regurgitation[b]	4.1%		
Moderate to severe transvalavular aortic regurgitation[c]	4.5%		

(a) Figures taken directly from table 1 in paper. Percentage figures are Kaplan-Meier estimates and p values are point in time estimates.
(b) As treated and with echocardiographic data (n= 73))
(c) As treated and with data on ejection fraction.(n=67)

3 years [6]

	TAVI	Standard therapy	p value
Repeat hospitalisation	43.5%	75.5%	<0.0001
Stroke	15.7%	5.5%	0.004
Myocardial infarction	4.1%	2.5%	0.59
Major vascular complications	17.4%	2.8%	HR 8.27 (95% CI 2.92 to 23.44) p<0.0001
Acute kidney injury	3.2%	11.1%	0.08
Major bleeding	32.0%	32.9%	0.92
Endocarditis	2.3%	0.8%	0.32
New pacemaker	7.6%	8.6%	0.75
Moderate to severe para-valavular aortic regurgitation[a]	4.5%		

(a) As treated and with echocardiographic data (n=44)

5 years [2]

	TAVI	**Standard therapy**	**Hazard Ratio**	**p value**
Repeat hospitalisation related to condition/valve	47.6%	87.3%	0.40 (95% CI 0.29 to 0.55)	<0.001
Stroke	16%	18.2%	1.39 (95%CI 0.62 to 3.11)	0.55

Abbreviations used: AVR, aortic valve replacement ; CI, confidence interval; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, Left ventricular ejection fraction;:NYHA, New York Heart Association; SF-12, Short Form 12 General Heath Survey;

Study 2: Mack MJ (2015) [7]

Mack MJ (2015) paper reports 5 year follow-up data. This table also draws on information presented in earlier papers by Smith CR (2011) [8], Reynolds NR (2012) [9] and Kodali SK (2012) [10]

Details

Study type	**Randomised control multicentre trial (PARTNER 1A)**
Country	USA, Canada and Germany
Recruitment period	2007 to 2009
Study population and number	n=**699** high risk operable patients **(TAVI n=348 versus SAVR n=351)**
Age and sex	**Mean 84.0 years** (TAVI 83.6±6.8; SAVR 84.5±6.4); 42.9% female (TAVI 42.2% female; SAVR 42.9%)
Patient selection criteria	Inclusion Criteria • Predicted risk of operative mortality was ≥15% and/or a STS score of ≥10; senile degenerative aortic valve stenosis; symptomatic due to aortic valve stenosis as demonstrated by NYHA Functional Class ≥II. Exclusion Criteria • life expectancy <12 months due to non-cardiac co-morbid conditions • recent acute myocardial infarction (≤1 month) or cerebrovascular accident or transient ischemic attack (within 6 months), renal insufficiency or end stage renal disease requiring chronic dialysis • aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified; mixed aortic valve disease • any therapeutic invasive cardiac procedure performed within 30 days or 6 months if the procedure was a drug eluting coronary stent implantation); pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, severe mitral regurgitation or Gorlin syndrome • blood dyscrasias, thrombocytopenia (platelet count <50,000 cells/mm³), history of bleeding diathesis or coagulopathy • untreated clinically significant coronary artery disease requiring revascularization • hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices • hypertrophic cardiomyopathy with or without obstruction, severe ventricular dysfunction with LVEF <20%, evidence of intracardiac mass, thrombus or vegetation • active peptic ulcer or upper gastro-intestinal bleeding within the prior 3 months. • a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately pre-medicated • native aortic annulus size < 18mm or > 25mm as measured by echocardiogram; significant abdominal or thoracic aorta disease; bulky calcified aortic valve leaflets in close proximity to coronary ostia • vessel characteristics that would preclude safe placement of introducer sheath • currently participating in an investigational drug or another device study • active bacterial endocarditis or other active infections
Technique	Patients who were assigned to TAVI had either transfemoral (n=244) or transapical (n=104) placement of the aortic valve (SAPIEN heart-valve system (Edwards Lifesciences)) under general anaesthesia. The decision on route was based on whether peripheral arteries could accommodate the large French sheaths needed (22 French for the 23-mm valve and 24 French for the 26-mm valve). Transapical placement was performed through a small intercostal incision over the left ventricular apex with the use of a dedicated delivery catheter. Patients received heparin during the procedure and dual antiplatelet therapy (aspirin and clopidogrel) for 6 months afterward. Control group received standard surgical care.
Follow-up	**5 years** (30 days, 6 months, 1 year, 2 and 5 years)
Conflict of interest/source of funding	Study supported by Edwards Life Sciences

Analysis

Follow-up issues: Patients were actively followed up with medical checks. 42 patients did not have their assigned procedure (4 in the TAVI group and 38 in the surgical group). Main reasons: withdrawal from the study or decided not to have surgical therapy. Completeness of follow-up is unclear.

Study design issues:

- 25 centres (22 in the USA).
- Severe aortic stenosis was defined as an aortic-valve area less than 0.8 cm^2 plus either a mean gradient of at least 40 mm^{Hg} or a peak velocity of at least 4.0 m per second.
- Patients were deemed to be a high risk for complications or death on the basis of coexisting conditions associated with risk of death of at least 15% within 30 days of the procedure.
- Patients in the TAVI group received heparin during the procedure and aspirin and clopidogrel for 6 months.
- 2 surgeons decided whether a patient was considered suitable.
- Computer-generated block randomisation. Serious events adjudicated by independent committee.
- All events reviewed once as blinded review and then unblended
- All analyses intention-to-treat.
- Authors calculated that 650 patients gave 85% power to show the non-inferiority of TAVI assuming 1-year mortality would be 29% in TAVI group compared with 32% in surgical group.
- Mean interval from randomisation to treatment were longer in the surgical group

The study was assessed to be at risk of having performance bias as there was no blinding of participants and personnel. The risk of selection bias is unclear.

Study population issues: There were no significant between-group differences in the characteristics at baseline.

Other issues: None.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **699 (348 TAVI vs 351 surgical replacement)**

Aborted procedure / conversion to open procedure in the TAVI group: 4.6% (16/348)

Death

	TAVI	Surgical	P valve
1 year			
Death (any cause)	84 (24.2%)	89 (26.8%)	0.44
Death (cardiovascular cause)c	47 (14.3%)	40 (13.0%)	0.63
2 years			
Death (any cause)	116 (33.9)	114 (35.0%)	0.78
Death (cardiovascular cause)c	67 (21.4)	59 (20.5)	0.80
5 years			
Mortality (all cause)	229 (67.8%)	198 (62.4%)	0.76
Mortality (cardiac related)	147 (53.1%)	123 (47.6%)	0.67

Functional outcome
NYHA class I and II

	TAVI (n=348)	Surgical (n=351)	P value
Baseline[i]	8	8	1.00
30 days[i]	72	58	<0.001
6 months[i]	70	64	0.05
1 year[i]	64	64	0.74
5 years	85/100	79/97	0.85

[i] Figures read by analyst from graph.

6-minute walk test At 30 days, patients in the transcatheter group could walk further than those in the surgical group (p = 0.002). At 1 year, patients in both study groups had an improvement in cardiac symptoms and the 6-minute walk distance, with no significant differences between groups reported.

Length of stay in the intensive care unit:
TAVI group: 3 days
Surgical group: 5 days (p < 0.001)

Length of stay in hospital:
TAVI group: 8 days
Surgical group: 12 days (p < 0.001)

Safety

3 patients in TAVI and 1 patient in surgical group died during the procedure.

30 days [8]

	TAVI (n=348)	Surgical (n=351)	P value
Death (any cause)	12 (3.4%)	22 (6.5%)	0.07
Death (cardiovascular cause)	11 (3.0%)	10 (12.8%)	0.9
Repeat hospitalisation	15 (4.4%)	12 (13.7%)	0.64
All strokes / TIA	19 (5.5%)	8 (2.4%)	0.04
Minor stroke	3 (0.9%)	1 (0.3%)	0.34
Major stroke	13 (3.8%)	7 (2.1%)	0.20
Major vascular complications	38 (11%)	11 (3.8%)	<0.001
Acute Kidney injury	10 (2.9%)	10 (3.0%)	0.95
Major bleeding	32 (9.3%)	67 (19.5%)	0.95
New atrial fibrillation	30 (8.6%)	56 (16.0%)	<0.006
New pacemaker	13 (3.8%)	12 (3.6%)	0.89
Endocarditis	0	1 (0.3%)	0.32

Moderate to severe paravalvular regurgitation

	TAVI (n=348)	Surgical (n=351)	P value
Baseline	12.2 (35/289)	0.9 (2/229)	<0.001
30 days	6.8 (15/222)	1.9 (3/159)	<0.001

Haemodynamic performance (on echocardiography) [8]

	n	TAVI	n	Surgical	P value
Mean aortic valve area (cm^2)					
Baseline	319	0.7±0.2	297	0.6±0.2	0.32
30 days	279	1.7±0.5	228	1.5±0.4	.001
6 months	235	1.7±0.5	165	1.5±0.5	0.01
1 year	219	1.6±0.5	155	1.4±0.5	0.002
Mean aortic valve gradient (mmHg)					
Baseline	327	42.7±14.5	301	43.5±14.3	0.51
30 days	287	9.9±4.8	231	10.8±5.0	0.04
6 months	246	10.2±4.3	170	10.8±4.8	0.16
1 year	227	10.2±4.3	159	11.5±5.4	0.008
LVEF					
Baseline	330	52.6±13.5	300	53.6±12.5	0.35
30 days	288	55.5±11.4	231	56.0±11.4	0.63
6 months	244	56.2±10.8	173	56.8±9.9	0.56
1 year	224	56.6±10.5	159	57.1±10.3	0.64

Quality of Life [9]

Mean change transfemoral TAVI vs surgical from baseline EQ5D score

		TAVI		Surgical	Mean Difference (95% CI)
1 month	192	0.08±0.25	154	0.02±0.25	0.06 (0.01 to 0.11)
6 month	176	0.1±0.3	136	0.09±0.27	0.01 (-0.05 to 0.07)
1 year	160	0.09±00.23	129	0.08±0.23	0.01 (-0.4 to 0.06)

Less than 0 favours SAVI

Mean change transapical TAVI vs surgical from baseline EQ5D score

		TAVI		Surgical	Mean Difference (95% CI)
1 month	74	-0.2±0.24	58	0.01±0.19	-0.03 (-0.10 to 0.04)
6 month	66	0.04 ± 0.27	52	0.06 ± 0.2	-0.02 (-0.10 to 0.06)
1 year	61	0.06 ± 0.22	54	0.05 ± 0.6	0.01 (-0.16 to 0.18)

Mean change transfemoral TAVI vs and surgical from baseline SF12 scores

			TAVI		Surgical	Mean Difference (95% CI)
1 month	Physical Mental	184	5.0 4.3	149	2.6 -0.3	2.0 (0.1 to -0.3) p=0.04 5.4 (3.1 to 7.7) p<0.001
6 month	Physical Mental	149	6.7 5.1	134	7.2 4.0	-0.9 (-3.0 to 1.2) p<0.41 1.2 (-1.0 to 3.5) p=0.28
1 year	Physical Mental	187	6.3 5.3	147	6.1 4.7	0.41 (-2.8 to 2.0) p=0.77 0.4 (-1.8 to 2.7) p=0.69

1 year [8]

	TAVI (n=348)	Surgical (n=351)	P value
Repeat hospitalisation	59 (18.6%)	45 (15.5%)	0.38
All strokes / TIA	28 (8.7%)	13 (4.3%)	0.04
Minor stroke	0.9%	0.7%	0.84
Major stroke	5.1%	2.4%	0.07
Vascular complications	39 (11.3%)	13 (3.8%)	<0.001
Renal failure	18 (5.4%)	20 (6.5%)	0.57
Major bleeding	49 (14.7%)	85 (25.7%)	<0.001
New atrial fibrillation	42 (12.1%)	60 (17.1%)	0.07
New pacemaker	19 (5.7%)	16 (5.0%)	0.68
Endocarditis	2 (0.6%)	3 (1.0%)	0.63

Note these figures are reported across a number of papers and there are some minor inconsistencies between figures reported.

2 year [10]

	TAVI (n=348)	Surgical (n=351)	P value
Repeat hospitalisation	74 (24.7%)	60 (21.7%)	0.41
All strokes / TIA	34 (11.2%)	18 (6.5%)	0.05
Stroke	24 (7.7%)	14 (4.9%)	0.17
Major vascular complications	40 (11.6%)	13 (3.8%)	<0.001
Renal failure	20 (6.2%)	21 (6.9%)	0.75
Major bleeding	60 (19.0%)	95 (29.5%)	0.002
MI	0	4 (1.5%)	0.05
New pacemaker	23/ (7.2%)	19 (6.4%)	0.69
Endocarditis	4 (1.5%)	3 (1.0)	0.61

5 year [7]

	TAVI (n=348)	Surgical (n=351)	P value
Repeat hospitalisation	108 (42.3%)	81 (34.2%)	0.17
All strokes / TIA	42 (15.9%)	33 (14.7%)	0.35
Stroke	29(10.4%)	26 (11.3%)	0.61
Major stroke	18/348	11/351	
Major vascular complications	41 (11.9%)	14 (4.7%)	0.0002
Renal failure	24 (8.6%)	24 (8.5%)	0.69

Mean change transapical TAVI vs surgical from baseline SF12 scores

			TAVI		Surgical	Mean Difference (95% CI)
1 month	Physical Mental	76	2.8 -0.8	61	0.5 1.7	-5.8 (-17.9 to 6.4) p=0.35 0.3 (-2.7 to 3.3) p=0.85
6 month	Physical Mental	70	5.2 3.3	57	5.7 3.7	-3.8 (-15.1 to 735) p=0.51 -3.36 (-6.7 to 0.0) p=0.05
1 year	Physical Mental	66	7.1 3.6	58	4.5 3.9	6.1 (5.9 to 18.1) p=0.32 0.2 (-3.5 to 3.8) p=0.92

Mean change transfemoral TAVI vs surgical from baseline KCCQ scores

		TAVI		Surgical	Mean Difference (95% CI)
1 month	196	31.5	154	18.9	9.8 (4.0 to 15.6) p=0.001
6 month	182	38.2	137	34.0	0.3 (-5.2 to 5.7) p=0.93
1 year	165	38.1	130	22.3	-1.9 (-7.6 to 3.7) p=0.50

Mean change transapical TAVI vs surgical from baseline KCCQ scores

		TAVI		Surgical	Mean Difference (95% CI)
1 month	77	22.1	61	20.9	-4.7 (-13.9 to 4.5) p=0.32
6 month	71	32.1	56	34.8	-8.4 (-17.0 to 0.2) p=0.06
1 year	65	41.7	58	29.5	4.8 (-4.0 to 13.17) p=0.28

Major bleeding	75 (26.6%)	103 (34.4%)	0.003
MI	5 (2.9%)	11 (5.9%)	0.15
New pacemaker	28 (9.7%)	23 (9.1%)	0.64
Endocarditis	5 (2%)	6 (2.5%)	0.65

Abbreviations used: CI, confidence interval; EQ5D, EuroQual 5 dimensions; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; SF-12 Short Form 12 General Heath Questionnaire; TAVI, transcatheter aortic valve implantation; TIA, transient ischaemic attack

Study 3 Deeb GM (2016) [11]

Deeb GM (2016) paper reports 3 year follow-up data. This table also draws on information presented in Adams DH (2014)[12] who report the first year of outcomes.

Details

Study type	**Randomised control multicentre trial (US Core Valve, also known as CoreValve US Pivotal trial or US Pivotal trial)**
Country	USA
Recruitment period	1.5 years (February 2011 to September 2012)
Study population and number	n=**795 high risk operable patients** were randomised (**394 TAVI** (330 iliofemoral patients and 64 noniliofemoral patients) **versus 401 SAVR**)
Age and sex	83.35 years (TAVI 83.2±7.1; SAVR 83.5±6.3); 46.7% (372/795) females (46.4% female TAVI; 47.1% female SAVR)
Patient selection criteria	• Patients with severe aortic stenosis and heart failure symptoms of New York Heart Association (NYHA) class II or higher were eligible for inclusion in the study if they were considered to be at increased risk for undergoing surgical aortic valve replacement. • Aortic stenosis was defined as an aortic-valve area of 0.8 cm^2 or less or an aortic- valve index of 0.5 cm^2 per square meter or less and either a mean aortic-valve gradient of more than 40 mm Hg or a peak aortic-jet velocity of more than 4.0 m per second. • Patients were considered to be at increased surgical risk if 2 cardiac surgeons and 1 interventional cardiologist at the investigative site estimated that the risk of death within 30 days after surgery was 15% or more and the risk of death or irreversible complications within 30 days after surgery was less than 50%. Surgical risk assessment included consideration of the Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) estimate and other factors not included in the STS PROM assessment. The STS PROM provides an estimate of the rate of death at 30 days among patients having surgical aortic-valve replacement on the basis of a number of demographic and procedural variables.
Technique	Patients assigned to surgical aortic-valve replacement were treated by means of conventional open-heart techniques with the use of cardiopulmonary bypass. The choice and size of the surgical prosthetic valve were left to the discretion of the surgeon. After the procedure, aspirin, at a dose of at least 81 mg daily, was given indefinitely in all the patients who underwent surgical valve replacement, including patients who continued to receive warfarin therapy. Patients assigned to TAVI received the CoreValve self-expanding prosthesis (Medtronic) either by iliofemoral or noniliofemoral route. Valve size was determined on the basis of a CT angiogram obtained before enrolment. Valve sizes were 23 mm (1.5%), 26 mm (31.4%), 29 mm (49.4%), and 31 mm (17.7%). Dual antiplatelet therapy with aspirin, at a dose of at least 81 mg daily, and clopidogrel, at a dose of 75 mg daily, was recommended before the procedure and for 3 months after the procedure, followed by aspirin or clopidogrel monotherapy at the same dose indefinitely. In the event that warfarin was indicated for other reasons, aspirin, at a dose of at least 81 mg daily, and warfarin were administered indefinitely without clopidogrel.
Follow-up	**3 years** (30 days, 6 months, 1 year, 2 years and 3 years)
Conflict of interest/source of funding	Study supported by Medtronic. Authors have disclosed relevant interests.

Analysis

Follow-up issues: The authors report using an as-treated analysis population to account for differential dropout of patients who declined therapy after randomisation, primarily open surgery; however, they also reported that the mortality benefit at 3 years with TAVI was similar in the intention-to-treat cohort.

The authors acknowledged that the limitation of a 3-year follow-up, ideally 10 years would be needed to understand the longer-term durability in patients at lower risk with longer life expectancies.

Study design issues: The study was powered to detect whether TAVI was superior to SAVR in avoided major adverse cardiovascular and cerebral events (MACCE) at 30 days or hospital discharge, whichever was longer.

Randomisation to the treatment arms was stratified by eligibility for iliofemoral access. The primary end point was the rate of death from any cause at 1 year. Data on 1 year, 2 years and 3 years outcomes were analysed.

The study was assessed to be at risk of having performance bias as there was no blinding of participants and personnel. The risk of selection bias is unclear.

Study population issues: There were no significant reported between-group differences in baseline characteristics, with the exception of status with respect to diabetes mellitus (p=0.02 in the intention-to-treat population, and p=0.003 in the as-treated population).

Among the 795 patients randomised in the study, 48 patients did not have the assigned treatment (TAVI, n=4; SAVR, 44). The reasons that no procedure was performed included death (TAVI, n=2; SAVR, n=5), patient withdrew consent (TAVI, n=1; SAVR, n=31); physician withdrew patient (TAVI, n=1; SAVR, n=5), patient refused treatment (SAVR, n=2) and patient met exclusion criteria 4+ mitral regurgitation prior to procedure (SAVR, n=1).

The authors report ‘as-treated’ rather than ‘intention to treat’ in their analysis. The author’s analysis is reported in the table below. The authors of the systematic review commissioned by NICE (study 8 below) used an intention-to-treat approach to their analysis.

Other issues: The authors stated they were uncertain whether the crimping–recrimping of the transcatheter valve would have an impact on long-term bioprosthesis durability.

Key efficacy and safety findings

Efficacy

Number of patients analysed:795**(394TAVI (330 iliofemoral and 64 noniliofemoral) versus 401 surgical replacement)**

Aborted procedure / conversion to open procedure in the TAVI group: 0.5% (12/394)

Death

	TAVI	SAVR	P valve
1 year			
Death (any cause)	55 (14.2%)	67 (19.1%)	0.04
Death (cardiovascular cause)	40 (10.4%)	44 (12.8%)	0.31
3 years			
Death (any cause)	125 (32.9%)	132 (39.1%)	0.068
Death (cardiovascular cause)	83 (22.9%)	85 (27.2%)	0.218

Functional outcome

NYHA class I and II		TAVI		SAVR	P value
Baseline	391	16.9%	352	18.2%	0.87
1 month	376	82.8%	331	73.4%	<0.001
6 months	363	83.7%	315	79.1%	0.04
1 year	365	78.9%	304	72.4%	0.10
2 years	255	92.1%	189	90.5%	-
3 years	195	92.3%	146	91.1%	-

P values are differences between SAVR and TAVI across all NYHA classes

Length of stay in the intensive care unit: Not reported
Length of stay in hospital: Not reported

Haemodynamic performance (on echocardiography)

	TAVI	SAVR	P value
Mean aortic valve area (cm^2)			
Baseline	0.66 ±0.22	0.67±0.25	n.s.
1 year	1.70 ±0.49	1.55 ±0.51	<0.001
3 years	1.79 ±0.48	1.53 ± 0.52	<0.0001
Mean aortic valve gradient (mmHg)			
Baseline	49.47 ±14.53	48.70 ±13.31	n.s.
1 year	8.90 ±3.73	12.17 ±7.10	<0.0001
3 years	7.62 ± 3.57	11.40 ± 6.8	<0.0001
Left Ventricular ejection fraction, %			
Baseline	56.9 ±12.5	56.0 ±12.2	n.s.
1 year	57.8 ±11.0	58.2 ± 8.9	n.s.
3 years	56.8 ± 1.0	58.0 ± 9.2	n.s.

Quality of Life (Arnold 2015)

Safety

Post implantation balloon valvuloplasty was performed in 20.3% of patients. There were no events of device migration or embolization. Two patients required emergent conversion to surgery due to coronary obstructions. A single patient (0.3%) underwent a concomitant percutaneous coronary intervention. Two valves were implanted in 4.1% of patients.

1 month

As treated population	TAVI (n=390	SAVR (n=357)	P value
Death (any cause)	13 (3.3%)	16 (4.5%)	0.43
Death (cardiovascular cause)	12 (3.1%)	16 (4.5%)	0.32
Re-intervention	3 (0.8%)	0 (0.0%)	0.10
Minor stroke	4 (1.0%)	13 (3.4%)	0.03
Major stroke	15 (3.9%)	11 (3.1%)	0.55
Cardiac shock‡	9 (2.3%)	11 (3.1%)	0.51
Cardiac perforation‡	5 (1.3%)	0	0.03
Major vascular complications ‡	23 (5.9%)	6 (1.7%)	0.003
Acute Kidney injury	23 (6%)	54 (15.1%)	<0.001
Major bleeding‡	109 (28.1%)	123 (34.5%)	0.05
New atrial fibrillation‡	45 (11.7%)	108 (30.5%)	<0.001
New pacemaker‡	76 (19.8%)	25 (7.1%)	<0.001

‡ Kaplin-Meier estimates

Moderate or severe paravalvular regurgitation

	TAVI	SAVR	P value
Baseline	Not assessed		
1 year	23/299 (7.7%)	3/232 (1.3%)	<0.001
3 years	11/188 (5.9%)	0/135 (0.0%)	<0.01

1 year (12)

As treated population	TAVI (n=390)	SAVR (n=357)	P value
Re-intervention	7 (1.9%)	0	0.01
Minor stroke	11 (3.0%)	20 (6.0%)	0.05
Major stroke	22 (5.8%)	23 (7.0%)	0.59
Cardiogenic shock‡	9 (2.3%)	11 (3.1%)	0.51
Cardiac perforation‡	5 (1.3%)	0	0.03
Major vascular complications	24 (6.2%)	136 (38.4%)	<0.001

Mean change from baseline EQ5D score

	n	TAVI	n	SAVR	Mean Difference (95% CI)
Transfemoral					
1 month	204	0.055±0.23	144	-0.073±0.26	0.13 (0.008 to 0.18)
6 month	221	0.053±0.22	173	0.04±0.17	0.01 (-0.03 to 0.05)
1 year	199	0.043±0.2	155	0.0003±0.02	0.04 (-0.00 to 0.08)
Non-transfemoral					
1 month	31	-0.082±0.27	25	-0.072±0.25	-0.01 (-0.15 to 0.13)
6 month	38	0.026±0.668	31	0.041±0.645	-0.02 (-0.33 to 0.30)
1 year	36	0.023 ± 0.17	27	0.046±0.14	-0.02 (-0.09 to 0.05)

Mean change from baseline SF12 score

			TAVI		SAVR	Mean Difference (95% CI)
Transfemoral						
1 month	Physical Mental	186	5.4 3.5	137	0 -2.9	4.9 (3.1 to 6.7) p<0.001 6.1 (3.8 to 8.5) p<0.001
6 month	Physical Mental	210	6.3 5.2	159	6.8 2.7	-0.3 (-2.1 to 1.4) p=0.77 0.4 (-1.8 to 2.7) p=0.69
1 year	Physical Mental	67	5.9 4.8	57	5.1 2.9	0.1 (-2.0 to 2.2) p=0.927 0.8 (-1.3 to 3.0) p=0.456
Non-transfemoral						
1 month	Physical Mental	29	1.7 -2.8	21	-1.0 0.4	3.2 (-0.09 to 7.4) p=0.126 -0.1 (-5.4 to 5.1) p=0.957
6 month	Physical Mental	38	6.3 0.026	32	3.4 2.8	0.1 (-0.35 to 3.7) p=0975 -1.0 (-5.0 to 2.69) p=0.609
1 year	Physical Mental	36	6.6 0.023	25	6.1 4.8	2.9 (-1.9 to 7.8) p=0.237 1.3 (-3.7 to 6.3) p=0.610

Mean change from baseline **KCCQ scores**

		TAVI		SAVR	Adjusted mean difference (95% CI)
Transfemoral					
1 month	207	30.3	147	10.2	19.0 (13.7 to 24.3) p<0.001
6 month	224	36.5	172	32.4	4.1 (-0.5 to 8.6) p=0.078
1 year	202	34.2	135	33.6	0.2 (-4.5 to 4.9) p=0.948
Non-transfemoral					
1 month	34	12.6	25	11.3	8.3 (-3.5 to 20.2) p=0.169
6 month	39	27.6	31	23.1	-2.3 (-11.8 to 7.2) p=0.638
1 year	36	22.8	26	31.1	-1.1 (-12.2 to 10.1) p=0.853

Acute Kidney injury	23 (6.0%)	54 (15.1%)	<0.001
Major bleeding‡	114 (29.5%)	130 (36.7%)	0.03
New pacemaker‡	85 (22.3%)	38 (11.3%)	<0.001
New or worsening atrial fibrillation ‡	60 (15.9%)	115 (32.7%)	<0.001

Percentages are Kaplan-Meier estimates.

3 year (11)

As treated population	TAVI	SAVR	P value
Aortic Valve hospitalisation	95 (27.6%)	64 (21.9%)	0.087
TIA	9 (2.6%)	6 (2.0%)	0.616
Minor stroke	18 (5.4%)	26 (8.5%)	0.080
Major stroke	29 (8.1%)	35 (11.8%)	0.180
Major vascular complications	27 (7.1%)	7 (2.0%)	0.0001
Acute Kidney injury	24 (6.2%)	54 (15.1%)	<0.001
Major bleeding	125 (32.8%)	139 (40%)	0.045
New pacemaker	102 (28.0%)	46 (14.5%)	<0.001
Endocarditis	3 (0.9%)	5 (1.7%)	0.346

Percentages are Kaplan-Meier estimates.

Abbreviations used: CI, confidence interval; EQ%D, EuroQuol 5 dimensions; NYHA, New York Heart Association, SAVR, surgical aortic value replacement; SF-12 Short Form 12 General Health Questionnaire; TAVI, Transcatheter aortic valve implantation; TIA, transient ischaemic attack transient

Study 4 Leon MB (2016) [13]

Details

Study type	**Randomised control multicentre trial (PARTNER 2A)**
Country	USA and Canada (57 centres)
Recruitment period	2 years (December 2011 through November 2013)
Study population and number	n=**2032 patients** with severe aortic stenosis classified as having intermediate- surgical risk **(1011 TAVI versus 1021 SAVR)**
Age and sex	Mean 81.6 years (TAVI 81.5 ±6.7;SAVR 81.7 ±6.7); 45.5% (924/2035) female.
Patient selection criteria	Inclusion Criteria – PARTNER 2 1. Senile degenerative aortic valve stenosis. 2. Patient was symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater. 3. The heart team agreed (and verified in the case review process) that valve implantation would likely benefit the patient. Additional Eligibility Criteria Specific to Cohort A 1. STS >4 or <4 if the Heart Team determines intermediate-risk patient profile with important comorbidities not represented in the STS risk score algorithm. 2. Heart team (including examining cardiac surgeon) agree on eligibility including assessment that TAVI or SAVR is appropriate. 3. Heart team agreed (a priori) on treatment strategy for concomitant coronary disease (if present). 4. Study patient agreed to undergo surgical aortic valve replacement (AVR) if randomized to control treatment.
Technique	Patients assigned to TAVI underwent either transfemoral (n=775) or transthoracic (n=236) placement of the Edwards balloon-expandable SAPIEN XT heart-valve (26 mm). Transthoracic placement used the same valve placed through either the transapical or transaortic access route. All the patients received aspirin (81 g) and clopidogrel (≥300 mg) before the procedure and heparin during the procedure; patients continued to take aspirin indefinitely and clopidogrel for a minimum of 1 month.
Follow-up	**2 years**
Conflict of interest/source of funding	Supported by Edwards Lifesciences.

Analysis

Follow-up issues: Study patients had clinical follow-up at discharge, 30 days, 6 months, 1 and 2 years and then annually thereafter for a minimum of 5 years. Telephone follow-up at the analysis close date and as needed to obtain up to date survival information for use in regulatory submissions.
The authors acknowledged that a longer follow-up period (up to 10 years) is needed to assess the durability of bioprosthetic transcatheter valves.

Study design issues: Randomisation to TAVI and SAVR was stratified by whether patients were suitable for transfemoral or transthoracic placement of the valve. Patients risk was assessed by a multidisciplinary heart team, based on the STS risk of death after 30 days. Included patients who had an STS of at least 4%, with an upper limit of 8% (applied by review committee, not pre-specified). Patients with a risk score of <4% could also

be enrolled if there were other conditions not represented in the risk model. The primary end point was death from any cause or disabling stroke at 2 years.
The study was assessed to be at risk of having performance bias because there was no blinding of participants and personnel. The risk of selection and reporting biases is unclear.

Study population issues: There were no significant between-group differences in the characteristics at baseline, except for peripheral vascular disease (p=0.02) and atrial fibrillation (p=0.05). Data on left ventricular ejection fraction was missing for 348 patients in the TAVI group and 347 in the surgery group.

Because of the higher frequency of unexpected withdrawals in patients randomised to SAVR (77 SAVR compared to 17 TAVI group) the authors compared their pre-specified analysis of the primary and secondary end points in the as-treated population with intention-to-treat analysis. This comparison was reported as revealing no important differences in the results.

Other issues:

- The SAPIEN XT valve that was used in this trial has already been replaced by the SAPIEN 3 valve system.
- Multi-slice computed tomography was not used consistently to assess aortic annulus dimensions for appropriate valve sizing.
- This trial did not systematically evaluate subclinical valve leaflet thrombosis using high-resolution imaging techniques.

Key efficacy and safety findings (PARTNER 2A)

Efficacy

Number of patients analysed: **2032 (1011TAVI (775 Transfemoral and 236 Transapical/TransAortic) versus 1021 surgical replacement)**

Aborted procedure / conversion to open procedure in the TAVI group: In 28 patients (1.4%; 20 patients in the TAVI group and 8 in the surgery group), the assigned procedure was initiated but the patient did not receive a valve implant.

Survival beyond 30 days

Death	TAVI(N = 1011)	SAVR (N = 1021)	P Value
1 year	N (%)	N (%)	
Death from any cause or disabling stroke	145 (14.5)	160 (16.4)	0.24
Death from any cause	123 (12.3)	124 (12.9)	0.69
Death from cardiac causes	70 (7.1)	77 (8.1)	0.4
2 years			
Death from any cause or disabling stroke	192 (19.3)	202 (21.1)	0.33
Death from any cause	166 (16.7)	170 (18.0)	0.45
Death from cardiac causes	97 (10.1)	104 (11.3)	0.38

	Transfermoral			**Transthoracic**		
	TAVI (n=775	**SAVR (n=775)**	**P value**	**TAVI (n=236)**	**SAVR (n=246)**	**P value**
1 Year N (%)						
Death (any cause)	77 (10.0)	90 (12.3)	0.17	46 (19.9)	34 (15.0)	0.17
Death (cardiovascular cause)	46 (6.0)	58 (8.0)	0.14	24 (10.8)	19 (8.5)	0.74
2 years N (%)						
Death (any cause)	108 (14.2)	124 (17.2)	0.11	55 (25.2)	46 (20.7)	0.26
Death (cardiovascular cause)	67 (9.0)	77 (10.9)	0.22	30 (13.7)	27 (12.7)	0.74

Safety

A total of **18 patients** (0.9%; 10 patients in the TAVR group and 8 in the surgery group) **died during the procedure or within 3 days afterward**.

30 days

	TAVI (N = 1011) N (%)	SAVR (N = 1021) N (%)	P Value
Death from any cause or disabling stroke	62 (6.1)	80 (8.0)	0.11
Death from any cause	39 (3.9)	41 (4.1)	0.78
Death from cardiac causes	33 (3.3)	32 (3.2)	0.92
Any stroke	55 (5.5)	61 (6.1)	0.57
Disabling stroke	32 (3.2)	43 (4.3)	0.2
Rehospitalisation	64 (6.5)	62 (6.5)	0.99
Myocardial infarction	12 (1.2)	19 (1.9)	0.22
Major vascular complication	80 (7.9)	51 (5.0)	0.008
Life-threatening or disabling bleeding	105 (10.4)	442 (43.4)	<0.001
Acute kidney injury	13 (1.3)	31 (3.1)	0.006
New atrial fibrillation	91 (9.1)	265 (26.4)	<0.001
New permanent pacemaker	85 (8.5)	68 (6.9)	0.17
Endocarditis	0	0	_
Aortic-valve re-intervention	4 (0.4)	0	0.05
Coronary obstruction	4 (0.4)	6 (0.6)	0.53

	Trans femoral			**Transthoracic**		
	TAVI (n=775) N (%)	**SAVR (n=775)** N (%)	**P value**	**TAVI (n=236)** N (%)	**SAVR (n=246)** N (%)	**P value**
Death (any cause)	23 (3.0)	31 (4.1)	0.24	16 (6.8)	10 (4.2)	0.21
Death (cardiovascular cause)	21 (2.7)	23 (3.0)	0.72	12 (5.2)	9 (3.8)	0.47
Rehospitalisation	42 (5.5)	47 (6.5)	0.44	22 (9.9)	15 (6.5)	0.20
All strokes / TIA	39 (5.1)	50 (6.5)	0.22	25 (10.7)	15 (6.2)	0.08
Minor stroke	14 (1.8)	16 (2.1)	0.70	9 (3.8)	2 (0.8)	0.03
Major stroke	18 (2.3)	32 (4.2)	0.04	14 (6.0)	11 (4.5)	0.348
MI	5 (0.6)	14 (8.1)	0.04	7 (3.0)	5 (2.1)	0.53

Functional outcome
NYHA class I and II (read from graph by reviewer)

		TAVI		SAVR	P value
Baseline	1011	22%	1020	23%	0.90
30 days	977	86%	875	82%	0.0013
1 year	938	81%	850	80%	0.97
2 years	899	74%	817	75%	0.97

Length of stay in the intensive care unit:
TAVI group: median 2 days
Surgical group: median 4 days (p<0.001)

Length of stay in hospital:
TAVI group: median 6 days
Surgical group: 1median 9 days (p<0.001)

Haemodynamic performance (on echocardiography)

	n	TAVI	n	SAVR	P value
Mean aortic valve area (cm2) (standard deviation)					
Baseline Transfermoral	775	0.7±0.2	755	0.7±0.2	n.s
Transthoracic	236	0.7±0.2	246	0.7±0.2	n.s.
30 days	890	1.7 ±0.5	788	1.5 ± 0.4	<0.001
1 year	751	1.6 ±0.4	633	1.4 ±0.4	<0.001
2 years	626	1.5 ± 0.4	536	1.4 ± 0.4	<0.001
Mean aortic valve gradient (mmHg) (standard deviation)					
Baseline Transfermoral	775	45.0±13.8	775	45.1±12.6	n.s.
Transthoracic	236	44.7±12.2	246	43.2±12.3	n.s.
30 days	890	9.7 ± 3.5	788	10.9 ± 4.3	<0.001
1 year	751	10.7 ±4.5	633	11.5 ±4.4	0.001
2 years	626	10.8 ± 4.6	536	11.7 ± 4.8	<0.001
Mean LVEF, % (standard deviation)					
Baseline Transfermoral	775	56.3±10.8	775	55.4±11.8	n.s
Transthoracic	236	56.2±10.9	246	55.1±12.3	n.s.
Average calculated by reviewer		56.3		55.3	
30 days	890	56.9 ±10.2	788	55.0±11.0	0.004
1 year	751	55.9±11.2	633	57.4±9.9	0.04
2 years	626	54.9 ±11.2	536	57.2 ±9.7	0.005

Major vascular complications	66 (8.5)	30 (3.9)	<0.001	14 (5.9)	21 (8.6)	0.26
Acute kidney injury (Stage 3)	4 (0.5)	23 (3.0)	<0.001	9 (3.9)	8 (3.4)	0.77
Major bleeding	52 (6.7)	320 (41.4)	<0.001	53 (22.6)	122 (49.8)	<0.001
New atrial fibrillation‡	38 (4.9)	204 (26.7)	<0.001	53 (22.8)	61 (25.4)	0.50
New pacemaker‡	62 (8.1)	54 (7.1)	0.49	23 (9.9)	14 (5.9)	0.11
Endocarditis	0	0		0	0	

Moderate to severe paravalvular regurgitation

	TAVI	SAVR	P value
30 days	4/872 (0.5%)	1/757 (0.1%)	n.s
1 year	4/728 (0.5)	0/611 (0.0%)	n.s
2 years	8/600 (1.3%)	1/514 (0.2%)	n.s

1 year

	TAVI (N=1011) N (%)	SAVR (N=1021) N (%)	P value
Any stroke	78 (8.0)	79 (8.1)	0.88
Disabling stroke	49 (5.0)	56 (5.8)	0.46
Rehospitalisation	142 (14.8)	135 (14.7)	0.92
Myocardial infarction	24 (2.5)	29 (3.0)	0.47
Major vascular complication	84 (8.4)	54 (5.3)	0.007
Life-threatening or disabling bleeding	151 (15.2)	460 (45.5)	<0.001
Acute kidney injury	32 (3.4)	48 (5.0)	0.07
New atrial fibrillation	100 (10.1)	272 (27.2)	<0.001
New permanent pacemaker	98 (9.9)	85 (8.9)	0.43
Endocarditis	7 (0.8)	6 (0.7)	0.84
Aortic-valve re-intervention	11 (1.2)	4 (0.5)	0.1
Coronary obstruction	4 (0.4)	6 (0.6)	0.53

	Transfermoral			**Transthoracic**		
	TAVI (n=775) N (%)	**Surgical (n=775)** N (%)	**P value**	**TAVI (n=236)** N (%)	**Surgical (n=246)** N (%)	**P value**
Rehospitalisation	97 (13.1)	104 (14.8)	0.34	45 (20.9)	31 (14.2)	0.07
All strokes / TIA	69 (9.2)	73 (10.0)	0.59	30 (13.1)	20 (8.6)	0.12
Minor stroke	21 (2.8)	20 (2.7)	0.92	9 (3.8)	4 (1.8)	0.18

Baseline date reported separately for two routes.

Major stroke	32 (4.3)	44 (6.0)	0.13	17 (7.5)	12 (5.0)	0.27
MI	14 (1.9)	23 (3.2)	0.13	10 (4.5)	6 (2.6)	0.29
Major vascular complicationsł	68 (8.8)	33 (4.3)	<0.001	16 (6.9)	21 (8.6)	0.49
Acute Kidney injury (Stage 3)	16 (2.2)	38 (5.2)	0.002	16 (7.3)	10 (4.3)	0.18
Major bleeding	84 (11.1)	333 (43.4)	<0.001	67 (29.1)	127 (52.3)	<0.001
New atrial fibrillation	45 (5.9)	210 (27.6)	<0.001	55 (23.8)	62 (25.9)	0.60
New pacemaker	73 (9.6)	69 (9.5)	0.93	25 (10.9)	16 (6.9)	0.13
Endocarditis	6 (0.8)	6 (0.9)	0.92	1 (0.5)	0	0.32

2 years

	TAVI (N=1011)	Surgery (N=1021)	P value
Any stroke	91 (9.5)	85 (8.9)	0.67
Disabling stroke	59 (6.2)	61 (6.4)	0.83
Rehospitalisation	183 (19.6)	156 (17.3)	0.22
Myocardial infarction	33 (3.6)	37 (4.1)	0.56
Major vascular complication	86 (8.6)	55 (5.5)	0.006
Life-threatening or disabling bleeding	169 (17.3)	471 (47.0)	<0.001
Acute kidney injury	36 (3.8)	57 (6.2)	0.02
New atrial fibrillation	110 (11.3)	273 (27.3)	<0.001
New permanent pacemaker	114 (11.8)	96 (10.3)	0.29
Endocarditis	11 (1.2)	6 (0.7)	0.22
Aortic-valve re-intervention	13 (1.4)	5 (0.6)	0.09
Coronary obstruction	4 (0.4)	6 (0.6)	0.53

	Transfermoral			**Transthoracic**		
	TAVI (n=775) N (%)	**Surgical (n=775)** N (%)	**P value**	**TAVI (n=236)** N (%)	**Surgical (n=246)** N (%)	**P value**
Rehospitalisation	131 (18.1)	116 (16.8)	0.52	52 (24.7)	40 (19.2)	0.18
All strokes / TIA	85 (11.6)	79 (11.0)	0.73	36 (16.4)	24 (11.0)	0.10
Minor stroke	24 (3.2)	21 (2.9)	0.67	9 (3.8)	6 (3.0)	0.62
Major stroke	39 (5.3)	48 (6.7)	0.60	20 (9.1)	13 (5.6)	0.16
MI	21 (3.0)	29 (4.2)	0.22	12 (5.6)	8 (3.8)	0.40

Major vascular complications	69 (9.0)	34 (4.5)	<0.001	17 (7.5)	21 (8.6)	0.65
Acute Kidney injury (Stage 3)	18 (2.5)	45 (6.5)	<0.001	18 (8.4)	12 (5.5%	0.23
Major bleeding	101 (13.6)	341 (44.7)	<0.001	68 (29.6)	130 (54.1)	<0.001
New atrial fibrillation‡	55 (7.4%)	211 (27.8)	<0.001	55 (23.8)	62 (25.9)	0.60
New pacemaker	85 (11.4%	77 (10.8)	0.71	29 (13.1)	19 (8.6)	0.13
Endocarditis	10 (1.5%)	6 (0.9)	0.33	1 (0.5)	0 (0.0%)	0.32

Abbreviations used: LVEF, left ventricular ejection fraction; MI, myocardial infarction; TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; TIA, transient ischaemic attack

Study 5 Sondergaard L 2016(14)

The Sondergaard L (2016) paper reports 2 year follow-up data. This table also draws on information presented in Thyregod HGH (2015)[15] who report the first year of outcomes.

Details

Study type	**Randomised control multicentre trial (NOTION)**
Country	Denmark and Sweden
Recruitment period	3 years (December 2009 to April 2013)
Study population and number	n=**280 low and intermediate surgical risk (145 TAVI versus 135 SAVR)**
Age and sex	Mean age: 79.1 years (TAVI 79.2±4.9; SAVR 79.0±4.7); 46% (131/280) female (TAVI 46.2% (67/145); SAVR 47.4% (64/135)
Patient selection criteria	Inclusion criteria • ≥70 years of age with severe degenerative aortic valve stenosis referred for SAVR and also candidates for TAVR were eligible for inclusion regardless of their predicted risk of death after surgery. • Severe aortic valve stenosis was defined as an effective orifice area <1 cm2 or indexed for body surface area <0.6 cm2/m2 and a mean aortic valve gradient >40 mm Hg or peak systolic velocity >4 m/s. • Symptomatic patients had to have dyspnea, New York Heart Association (NYHA) functional class II or higher, angina pectoris, or cardiac syncope to qualify for the trial. • Asymptomatic patients could be included if they had left ventricular posterior wall thickness ≥17 mm decreasing left ventricular ejection fraction, or new onset AF • Eligible patients were expected to survive for more than 1 year. Exclusion criteria • If they had another severe heart valve disease or coronary artery disease (CAD) requiring intervention. • Previous cardiac surgery. • Myocardial infarction (MI) or stroke within 30 days. • Severe renal failure requiring dialysis, or pulmonary failure with a forced expiratory volume within 1 s or diffusion capacity <40% of expected.
Technique	Patients randomized to TAVR received the Core-Valve self-expanding bioprosthesis (Medtronic Inc., Minneapolis, Minnesota) in sizes 23 mm, 26 mm, 29 mm, or 31 mm under general or local anaesthesia. The preferred route of arterial access was femoral 137, 96.5%), with left subclavian access as the second choice. Patients received a loading dose of pre-procedural clopidogrel (300 mg) and aspirin (75 mg) and unfractionated heparin during the procedure. Post-procedure, patients continued on a maintenance dose of clopidogrel (75 mg/day) for 3 months and lifelong aspirin (75 mg/day). Patients randomized to SAVR underwent conventional open heart surgery with the use of cardiopulmonary bypass. All patients received a bioprosthesis, with the specific type and size determined during the surgical procedure.
Follow-up	**2 years** (1, 6, 12 and 24 months)
Conflict of interest/source of funding	Authors acknowledge support from Medtronic.

Analysis

Follow-up issues:

- Follow-up assessments, including a physical examination, documentation of trial-specified outcomes and adverse events, NYHA functional classification, blood sampling, and 12-lead electrocardiography, were done before discharge and 1 month, 3 months, and 12 months after the procedure. Specially trained

echocardiographic technicians performed transthoracic echocardiograms at baseline and after 3 and 12 months.

- National electronic medical records were used to confirm clinical outcomes.

Study design issues:

- A heart team with at least an imaging cardiologist, an interventional cardiologist and a cardiac surgeon evaluated all patients, but predicted risk of death did not determine eligibility (Thyregod et al. 2015).
- The trials included all-comers, however the patients' mean STS score was 3.0 and 81.8% of the recruited patients were considered as of low-risk.
- The primary outcome was the composite rate of death from any cause, stroke, or myocardial infarction at 1 year. Data on 1 year and 2 years outcomes were analysed. The analysis for the primary outcome was performed in the intention-to-treat population with logistic regression to adjust for age, trial site, and history of CAD.
- Exploratory outcomes were as follows: the rate of individual components of the composite outcome; the rate of cardiovascular death; prosthesis re-intervention; cardiogenic shock; valve endocarditis; conduction abnormalities requiring permanent pacemaker; atrial fibrillation or flutter; and vascular, renal, and bleeding complications after1 and 12 months.
- Several outcomes were assessed un-blinded and therefore subject to bias. The sample size may have been too small to detect a potential difference in treatment effect on the primary outcome. The study was assessed to be at risk of performance and reporting biases. Unclear selection bias risk due to lack of description of random sequence generation.

Study population issues:

- No statistical significant differences between groups were found for any variables at baseline.

Other issues: The authors identified the following limitations:

- External validity was limited as only 3 centres recruited patients and therefore findings cannot be extrapolated to TAVI in general.
- The NOTION trial did not recruit patients with significant concomitant coronary artery disease, and outcomes for this large patient population cannot necessarily be inferred from the current trial.
- Formal neurological assessments were not performed in all patients, and more subtle neurological symptoms (for example, cognitive dysfunction) could have been overlooked.

Key efficacy and safety findings (NOTION)

Efficacy

Number of patients analysed: **276 (142 TAVI versus 134 surgical replacement)**

Aborted procedure / conversion to open procedure in the TAVI group: A total of 139 and 135 patients had the trial TAVI and SAVR prosthesis implanted, respectively. The arterial access was femoral in 96.5% of TAVI treated patients. 2 patients (1 in each group) were crossed over to the other procedure before an attempted procedure

Death

	TAVI(n=142)	SAVR(n=134)	P value
1 year N,%			
ITT (all deaths)	10/145 (6.9)	12/135 (8.9)	0.57
Death (any cause)	7 (4.9)	10 (7.5)	0.38
Death (cardiovascular cause)	6 (4.3)	10 (7.5)	0.25
2 years N, %			
Death (any cause)	11 (8.0)	13 (9.8)	0.54
Death (cardiovascular cause)	9 (6.5)	12 (9.1)	0.40

Functional outcome NYHA class I and II (calculated by analyst)

	TAVI	SAVRI	P value
Baseline	74/141 (52.5%)	73/133 (54.9%)	0.99
3 months	128/135 (94.8%)	111/115 (96.5%)	0.23
1 year	128/132 (96.9%)	116/120 (96.7%)	0.01
2 years	119/123 (96.7%)	110/114 (96.4%)	0.44

Length of stay in the intensive care unit: not reported
Length of stay in hospital: Not reported
Haemodynamic performance (on echocardiography)

	TAVI (n=142)	SAVR (n=134)	P value
Mean aortic valve area (cm2)			
Baseline	0.7	0.7	<0.001
3 months	1.7	1.4	<0.001
1 year	1.7	1.3	<0.001
2 years	1.6	1.3	<0.001
Mean aortic valve gradient (mmHg)			
Baseline	43.4	44.9	n.s
3 months	8.3	12.2	n.s
1 year	8.6	12.5	n.s
2 years	13.0	9.0	n.s.

P valves are differences in change between TAVI and SAVR from baseline

Quality of Life
Not reported or listed as outcome.

Safety

4 died before procedure (3 TAVI, 1 SAVR). 1 crossing from SAVR to TAVI died after 11 days.

30 days Kaplan Meier estimates (as treated analysis)

	TAVI (n=142)n(%)	SAVR (n=134) n (%)	P value
Death (any cause)	3 (2.1)	5 (3.7%	0.43
Death (cardiovascular cause)	3 (2.1)	5 (3.7)	0.43
All strokes / TIA	4 (2.8)	4 (3.0)	0.94
Stroke	2 (1.4)	4 (3.0)	0.37
Major vascular complications	8 (5.6)	2 (1.5)	0.10
Acute Kidney injury stage 2 or 3	1 (0.7)	9 (6.7)	0.01
Major bleeding	16 (11.3)	28 (20.9)	0.03
Cardiogenic shock	6 (4.2)	14 (10.4)	0.05
New or worsening atrial fibrillation	24 (16.9)	77 (57.8)	<0.001
MI	4 (2.8)	8 (6.0)	0.20
New pacemaker	46 (34.1)	2 (1.6)	<0.001
Valve Endocarditis	1 (0.7)	0	0.33

Moderate to severe aortic valve regurgitation

		TAVI		SAVR	P value
3 months	124	15.3%	111	21.6%	<0.001
1 year	121	15.7%	113	0.9%	<0.001

1 year (as treated analysis)	**TAVI** (n=142)	**SAVR** (n=134)	**P value**
All strokes / TIA	7 (5.0)	8 (6.2)	0.68
Stroke	4 (2.9)	6 (4.6)	0.44
New or worsening atrial fibrillation	30 (21.2)	79 (59.4)	<0.001
MI	5 (3.5)	8 (6.0)	0.33
New pacemaker	51 (38.0)	3 (2.4)	<0.001
Valve Endocarditis	4 (2.9)	2 (1.6)	0.47
2 year (as treated analysis)			
All strokes / TIA	13 (9.7)	10 (7.8)	0.67
Stroke	5 (3.6)	7 (5.4)	0.46
New or worsening atrial fibrillation	32 (22.7)	80 (60.2)	<0.001
MI	7 (5.1)	8 (6.0)	0.69
New pacemaker	55 (41.3)	5 (4.2)	<0.001

Abbreviations used: MI, myocardial infarction; NS, Non-significant: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; TIA, transient ischaemic attack.

Study 6 – Gargiulo G (2016) [16]

Details

Study type	Systematic Review
Country	Italy
Publication period	April 2002 (first-in-human TAVI date) until 5 April 2016. Databases searched Medline, Cochrane, Scopus, Google Scholar and following websites (www.clinicaltrials.gov, www.clinicaltrialresults.org, www.tctmd.com, www.cardiosource.org, www.theheart.org and www.escardio.org) and conference proceedings were checked.
Study population and number	**16,638** patients included in **5 RCTs** (NOTION (study 5), PARTNER 1A (study 2), PARTNER 2A (study 4), STACCATO, US CoreValve (study 3)) and **31 observational matched studies** who were considered inoperable or were at low- to intermediate to-high- surgical risk. The study included a sub-analysis of **6875 patients** who were considered to be at **low- to intermediate- surgical risk** from 2 RCTs and 6 observational studies reported here.
Age and sex	Information not provided.
Study selection criteria	Included • Randomised or observational matched studies were included if they reported mortality data of adult patients with severe aortic stenosis treated with TAVI versus SAVR. • Matched studies had to have TAVI and SAVR groups matched for propensity score or preoperative variables to minimize the effect of baseline confounding factors. Excluded • A study was excluded if any of the following criteria applied: o reported observational unmatched data (no type of matching was used to account for differences in preoperative characteristics); o it was a duplicate publication; o or the mortality outcome was not reported or could not be derived from the published results.
Technique	The review included all TAVI techniques (transfermoral, transapical, trans aortic) which were compared against SAVR
Follow-up	The study's focus was on primary outcomes were early (≤30 days), midterm (≤1 year) all-cause mortality. Though it look at longer term mortality (≥ 1 year) where data was reported.
Conflict of interest/source of funding	The authors were funded by their academic institutions. One author declared grants from the CardioPath PhD Program and European Association of Percutaneous Coronary Interventions. One author was a consultant for Edwards Lifesciences. Other authors declared no conflict of interest.

Analysis

Follow-up issues: None, because this is a systematic review, which focused on early (≤30 days), midterm (≤1 year) outcomes.

Study design issues: Gargiulo et al. (2016) asked clear questions. A published protocol was followed; appropriate databases, registries, web sites and scientific meeting presentations were searched, applying no language limits. Two people independently extracted data and assessed risk of bias using the Cochrane tool for RCTs and Newcastle Ottawa Scale for observational studies.

Study population issues: The study included a wide spectrum of patients with different surgical risk profiles. A sub analysis was produced for patients regarded as low-to-intermediate surgical risk on for all-cause mortality but not early (≤30 days) cardiovascular mortality, stroke, MI, pacemaker implantation, vascular complications, paravalvular leak, major bleeding, acute kidney injury and new onset atrial fibrillation.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>An analysis of 6875 patients with low- to intermediate-surgical risk (3501 TAVI, 3374 SAVR) from 2 RCTs and 6 observational studies reported here on all-cause mortality.

Mortality

<table><tr><th></th><th>Odds ratio</th></tr><tr><td>1 year</td><td>0.91 (95% CI 0.67 to 1.23) p=0.47</td></tr><tr><td>Long term (>1year)</td><td>1.06 (95% CI 0.59 to 1.91 p=0.70</td></tr></table>Less than 1 favours TAVI</td><td>30 day mortality

OR 0.67 (95% CI 0.42 to 1.07) p=0.08 (Less than 1 favours TAVI)</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval, OR, odds ratio; SAVR, surgical aortic valve replacement; TAVI, Transcatheter aortic valve replacement</td></tr>
</table>

Study 7 – Siemieniuk RA (2016) [17]

Details

Study type	Systematic review
Country	Canada, Switzerland, Poland and USA
Publication period	2012 to 2016; databases searched: Medline, Medline in-process, Embase, and Cochrane CENTRAL
Study population and number	**3179 patients with low to intermediate surgical risk** (risk score of 8% or less) participating in 4 RCTs (NOTION (study 5), PARTER 2A (Study 4), STACCATO, US CoreValve (study 3)
Age and sex	n/a
Study selection criteria	Randomised trials of TAVI compared with SAVR in patients with a mean perioperative risk of death <8%.
Technique	Included studies compared SAVR against TAVI using range of procedures including femoral, left subclavian, Transfermoral / femoral, transthoracic. Iliofemoral, non-illofermoral
Follow-up	This review focused on outcomes reported at 2 years by included studies.
Conflict of interest/source of funding	The authors declared they had received no support from any organization for the study; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Analysis

Follow-up issues: The authors identified the relatively short duration of follow-up in studies included in their review as causing uncertainty about one need for re-intervention over the longer term where patients have received TAVI valves.

Study design issues: Two patients worked with the study advisory panel to list the outcomes that were important to them and highlighted pain and recovery time as critical to decision making which no information was available in included studies.

Study population issues: The authors identified the following limitations:

- The modest total number of patients (3179) and questionable generalization of results to low risk patients (most patients were at intermediate rather than low surgical risk); the review includes the US CoreValve study population which could be described as high risk as the inclusion criteria specified at least 15% predicted operative mortality risk.
- The randomized controlled trials used bioprosthetic valves, typically used in older patients, in all SAVRs. Therefore results only to relate patients who have already chosen to use a bioprosthetic valve instead of a mechanical valve.

Other issues: The authors identified the following issues:

- They were not able to ascertain how much of the increased risk of atrial fibrillation with SAVR represents transient postoperative atrial fibrillation; this is less important for patients than persistent atrial fibrillation.
- No trial included in their review reported recovery time (beyond length of hospital stay) or pain after the intervention, two outcomes that patient representatives had identified as important.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **3128 patients in 4 studies**

2 years mortality

	N	Hazard ratio	Absolute effect estimate (per 1000)	
			SAVR	TAVI
Transfemoral	2576 (3 studies)	0.79 (0.66 to 0.94)	152	122
Transapical	552 (2 studies)	1.34 (0.91 to 1.97)	196	253

Hazard rations less than 1 favours TAVI

Quality of Life

	N		SAVR	TAVI
HRQOL KCCQ scale 0 to 100 (high better)	795 (1 study)	Average improvement on baseline	18.7	22.2

Safety

30 day mortality

OR 0.67 (95% CI 0.42 to 1.07)

2 year follow up

	N	Odds ratio / Relative Risk	Absolute effect estimate (per 1000)	
			SAVR	TAVI
Stroke by route				
Transfemoral	2576 (3 studies)	RR 0.80 (0.63 to 1.01)	99	79
Transapical	552 (2 studies)	RR 1.67(0.97 to 2.87)	67	112
Acute Kidney injury by route				
Transfemoral	2576 (3 studies)	RR 0.38 (0.27 to 0.54)	85	32
Transapical	552 (2 studies)	RR 1.54 (0.77 to 3.07)	43	66
Major bleeding by route				
Transfemoral	2576 (3 studies)	RR 0.39 (0.29 to 0.54)	413	161
Transapical	552 (2 studies)	RR 0.53 (0.42 to 0.67)	413	219
Not reported by route				
Atrial fibrillation	3058 (3 studies)	RR 0.43 (0.35 to 0.52)	312	134
NYHA class III or IV	2146 (4 studies)	OR 1.29 (1.08 to 1.55)	330	389
Aortic valve re-intervention	3058 (4 studies)	RR 3.25 (1.29 to 8.14)	3	10
Permanent pacemaker	3128 (4 studies)	RR 2.46 (1.17 to 5.15)	92	226
Myocardial infarction	3128 (4 studies)	RR 0.87 (0.59 to 1.29)	36	31

OR and RR less than 1 favours TAVI

Abbreviations used: HRQOL, health related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire ;NYHA, New York Heart Association; OR, odds ratio; RR, relative risk; SAVR surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

Study 8 – Lui Z (2017) [1]

This study was a systematic review commissioned by NICE to support the production of this overview. Studies 1 to 7 above were included in this review. The study pooled data for outcomes across studies where it possible to do so. The findings of pooled analyses are reported below. A paper is being prepared for publication.

Details

Study type	Systematic review
Country	United Kingdom
Publication period	2011 to 2016 databases searched The Cochrane Library, CRD Centre for Reviews and Dissemination Databases (DARE, NHS EED and HTA), MEDLINE, MEDLINE in Process, EMBASE, ZETOC and PubMed
Study population and number	This review covered patients ranging from low to high surgical risk and those considered inoperable using SAVR.
Age and sex	n/a
Study selection criteria	Published studies reporting the safety and efficacy of TAVI compared with standard therapies or no intervention for aortic stenosis were sought, including systematic reviews, randomised controlled trials, matched or non-matched studies, and non-comparative studies reporting longer term or important safety outcomes which were not covered by the comparative studies
Technique	Included studies compared TAVI using range of procedures including femoral, left subclavian, Transfermoral / femoral, transthoracic. Iliofemoral, non-illofermoral against standard medical care in inoperable patients and SAVR in patients who were classified as having high, intermediate or low surgical risk.
Follow-up	This review included studies that reported up to 5 years.
Conflict of interest/source of funding	The study was funded by NICE and the authors have no financial relationships with other organisation or conflicts of interest.

Analysis

Follow-up issues: This was a systematic review that assessed efficacy and safety of TAVI against standard therapy for patients stratified by surgical risk. Length of follow up varies by study as does reporting of outcomes with shorter duration of follow up for patients consider to have lower surgical risk.

Study design issues:

This systematic review only included comparative studies to assess efficacy but did include non-comparative studies to identify rare and significant events which are listed at the end of the summary on safety below.

The study used intention-to-treat analysis (ITT) approach. Where original studies included in the review reported figures based on as treated analysis these were recalculated using ITT approach.

Study population issues:

Patient populations were stratified by surgical risk.

Other issues:

None

Key efficacy and safety findings

For brevity and to avoid repeating findings reported in other studies described above, the table below only reports on outcomes where it was possible to pool data across two or more studies. The figures given below pool data from studies 2 and 3 described above for patients consider suitable for surgery but pose high risk.

Efficacy

Survival (beyond 30 days) in patients considered suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 year			
All cause	742	752	0.89 (0.73 to 1.09) p=0.26
Cardiovascular	742	752	1.05 (0.79 to 1.39) p= 0.73
2 years			
All cause	742	752	0.95 (0.79 to 1.13) p=0.55
Cardiovascular	742	752	0.92 (0.67 to 1.28) p=0.79

Less than 1 favours TAVI

Quality of life measured by EQ5D in patients suitable for surgery but high risk

	TAVI	SAVR	Mean Difference (95% CI)
Transfemoral			
1 month	396	298	0.09 (01.03 to 0.16) p=0.0006
6 month	397	309	0.01 (-0.02 to 0.05) p=0.47
1 year	359	284	0.03 (-0.00 to 0.06) p=0.09
Non-transfemoral			
1 month	105	83	-0.03 (-0.09 to 0.04) p= 0.44
6 month	104	84	-0.02 (-0.10 to 0.07) p= 0.66
1 year	97	81	-0.02 (-0.09 to 0.05) p= 0.58

Greater than 0 favours TAVI

Safety

Mortality (30 days) in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
All cause	742	752	0.64 (0.38 to 1.39) p=0.06
Cardiovascular	742	752	0.90 (0.52 to 1.56) p=0.70

Less than 1 favours TAVI

All stroke in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	1.26 (0.56 to 2.86) p=0.57
1 year	742	752	1.21 (0.49 to 2.98) p=0.68
2 year	742	752	1.11 (0.51 to 2.41) p=0.78

Less than 1 favours TAVI

Minor stroke in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	0.81 (0.10 to 6.59) p=0.84
1 year	742	752	0.61 (0.15 to 2.53) p=0.49
3 years	742	752	1.43 (0.22 to 9.28) p=0.71

Less than 1 favours TAVI

Transient ischemic attack in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	3.04 (0.62 to 15.01) p=0.17
1 year	742	752	1.46 (0.63 to 3.41) p=0.38
2 years	742	752	1.92 (0.90 to 4.11) p=0.09

Less than 1 favours TAVI

Quality of life measured by KCCQ in patients suitable for surgery but high risk

	TAVI	SAVR	Mean Difference (95% CI)
Transfemoral			
1 month	407	306	14.86 (8.47 to 21.21) p<0.00001
6 month	413	314	2.15 (-1.80 to 6.12) p=0.28
1 year	370	299	12.20 (-7.69 to 32.10) p=0.23
Non-transfemoral			
1 month	111	86	-0.56 (-8.701 to 7.58) p=0.89
6 month	110	89	3.00 (-8.90 to 6.14) p=0.72
1 year	104	85	-2.43 (-23.49 to 18.63) p=0.82

Greater than 0 favours TAVI

Major bleeding in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	0.67 (0.36 to 1.25) p=0.21
1 year	742	752	0.73 (0.48 to 1.12) p=0.02
2 years	742	752	0.78 (0.54 to 1.13) p=0.19

Less than 1 favours TAVI

Moderate or severe aortic regurgitation in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 year	502	435	4.02 (1.99 to 8.11)

Less than 1 favours TAVI

Major vascular complications in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	3.04 (0.63 to 3.41) p=0.17
1 year	742	752	1.46 (0.63 to 3.41) p=0.38
2 years	742	752	1.92 (0.90 to 4.11) p=0.09

Less than 1 favours TAVI

Permanent pacemaker implantation in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	1.94 (0.70 to 5.34) p=0.20
1 year	742	752	1.75 (0.94 to 3.25) p=0.08
2 years	742	752	1.77 (0.95 to 3.30) p=0.07

Less than 1 favours TAVI

Acute Kidney injury in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	0.51 (0.27 to 0.98) p=0.04
1 year	742	752	0.76 (0.23 to 2.59) p=0.67
2 years	742	752	0.64 (0.31 to 1.34) p=0.24

Less than 1 favours TAVI

Myocardial infarction in patients suitable for surgery but high risk

	TAVI	SAVR	Risk Ratio (95% CI)
1 month	742	752	0.72 (0.17 to 2.94) p=0.64
1 year	742	752	1.18 (0.42 to 3.29) p=0.76
2 years	742	752	0.51 (0.06 to 4.05) p=0.52

Less than 1 favours TAVI

Abbreviations used: CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; SAVR surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

Efficacy

Survival beyond 30 days

A randomised controlled trial (RCT) of 358 patients (PARTNER 1B) for whom surgical aortic valve replacement (SAVR) was unsuitable compared TAVI (n=179) with medical management (n=179). Patients who had TAVI had significantly lower all-cause mortality and cardiovascular mortality compared with medical management at a follow-up of 1, 2 and 5 years (30% compared with 51% at 1 year, 43% compared with 68% at 2 years and 72% compared with 94% at 5 years for all-cause mortality and 20% compared with 45% at 1 year, 31% compared with 62% at 2 years and 58% compared with 86% at 5 years for cardiovascular mortality [2; 3; 5; 6].

In an RCT of 795 patients for whom SAVR was suitable but high risk (the US CoreValve trial), a Kaplan-Meier cumulative probability analysis for all-cause mortality at 3 years follow-up was 33% for TAVI compared with 39% for SAVR (p=0.068) (11). In another RCT of 699 patients for whom SAVR was suitable but high risk (the PARTNER 1A trial), a Kaplan–Meier probability analysis for all-cause mortality up to 5 years of follow-up was 68% for TAVI compared with 62% for SAVR (p=0.76 When data were pooled for both RCTs (based on an intention-to-treat [ITT] analysis), the risk ratios did not show statistically significant differences between TAVI and SAVR for hazard of death (pooled estimates were risk ratio [RR] 0.89; 95% confidence interval [CI] 0.73 to 1.09, p=0.26 at 1 year and RR 0.95; 95% CI 0.79 to 1.13, p=0.55 at 2 years). There were no significant differences for cardiovascular mortality at 1 year (RR 1.05; 95% CI 0.79 to 1.39, p=0.73) and 2 years (RR 1.03; 95% CI 0.82 to 1.29, p=0.79)[1].

In an RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (the PARTNER 2A trial) there were no significant differences between TAVI and SAVR at 1- and 2-years follow-up for all-cause mortality and cardiovascular mortality (all-cause mortality: 12% compared with 13% [p=0.69] at 1 year and 17% compared with 18% [p=0.45] at 2 years; cardiovascular mortality: 7% compared with 8% [p=0.47] at 1 year and 10% compared with 11% [p=0.38] at 2 years)[13].

An RCT of 276 patients for whom SAVR was suitable but low to intermediate risk (the NOTION study) there were no significant difference in survival between TAVI and SAVR at 1- and 2-years follow-up for all-cause mortality and cardiovascular mortality (all-cause mortality: 5% compared with 8% [p=0.38] at 1 year and 8% compared with 10% [p=0.54] at 2 years; cardiovascular mortality: 4% compared with 8% [p=0.25] at 1 year and 7% compared with 9% [p=0.40] at 2 years)[14].

A systematic review including 2 RCTs and 6 observational studies representing 16,638 patients included an analyses of patients for whom SAVR was suitable and not high risk (comprising 6,875 patients in an analysis) showed little difference between TAVI and SAVR at 1 year (odds ratio [OR] 0.91, 95% CI 0.67 to 1.23) and long-term (more than 1 year) (OR 1.06, 95%CI 0.59 to 1.91)[18].

A systematic review of patients for whom SAVR was suitable but low and intermediate risk included 4 RCTs (n=3,179 patients, including the CoreValve pivotal trial), in which patients had a mean STS risk score of 7% reported that TAVI was associated with a lower hazard of death at 2 years compared with SAVR when done by the transfemoral but not transapical route (transfemoral route: hazard ratio [HR] 0.79, 95% CI 0.66 to 0.94, [risk difference −3.0, 95% CI −0.8 to −4.9]; transapical route: HR 1.34, 95% CI 0.91 to 1.97)[19].

Symptomatic improvement

In the RCT of 358 patients (PARTNER 1B) for whom SAVR was unsuitable, compared TAVI (n=179) with medical management (n=179). More patients were asymptomatic or had mild symptoms (New York Heart Association [NYHA] class I or II) in the TAVI group than those in the medical management group (at 2 years: 83% [79/95] compared with 42% [17/40]; p<0.001; at 3 years: 70% [49/70] compared with 50% [7/14], p=0.245 and at 5 years: 85.7% [42/49] compared with 60% [3/5], p=0.531; NYHA class was not significantly different at baseline among these groups)[6].

In the RCT of 795 patients for whom SAVR was suitable but high risk (CoreValve trial), a greater proportion of patients were in NYHA class I or II in the SAVR arm (73%; 79%) than in the TAVI arm (83%; 84%) (p<0.001; p=0.04) at 1 and 6 months but at 12 months

there were no statistically significant differences between the SAVR and TAVI groups (79% compared with 72%, p=0.10) [12]. In the other RCT of 699 patients for whom SAVR was suitable but posed a high risk (PARTNER 1A trial), the proportion of patients in NYHA class I or II was the same for TAVI (64%) and SAVR (64%) at 12 months[7].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A) there were no significant differences between TAVI and SAVR in proportion of patients in classes I and II at 1- and 2-year follow up[13].

An RCT of 276 patients for whom SAVR was suitable but intermediate risk (NOTION) there were no significant differences between TAVI and SAVR in NYHA class of patients at 3-months and 2-years follow-up[14].

The systematic review (4 studies; n=2,146) of patients for whom SAVR was suitable but low to intermediate risk found that TAVI was associated with an increased risk of heart failure symptoms (NYHA class III or more OR 1.29 (95% CI 1.08 to 1.55) at 2-year follow-up compared with SAVR. The certainty of this finding was graded as high. The OR for moderate or severe heart failure symptoms (NYHA III or more) was 1.29 (95% CI 1.08 to 1.55) and the certainty of this finding was graded as moderate (serious imprecision) [19].

Haemodynamic improvement

The RCT of 358 patients for whom SAVR was unsuitable, compared TAVI (n=179) with medical management (n=179). There was a significantly higher mean aortic valve area in the TAVI group than in the medical management group at 1-year follow-up (1.6 cm^2 [SD 0.5] compared with 0.7 cm2 [SD 0.3], p<0.001; baseline values were not significantly different). Mean pressure gradient improved from baseline (44.7 mmHg [SD 15.4]) to 13.2 (SD 11.2) for TAVI and from 43.2 (SD 15.4) to 44.3 (SD 16.1) for medical management (p values not reported). Left ventricular ejection fraction (LVEF) improved from 53.9 (SD 13.1) at baseline to 57.2 (SD 10.6) for TAVI and 51.2 (SD 14.3) to 56.9 (SD 10.3) for medical management respectively[6]. At 2 years the median and interquartile range values were reported for the TAVI group only for aortic valve area

(1.53 cm^2; interquartile range [IQR] 1.28-1.85), mean pressure gradient (9.7mmHg [IQR 7.7 to 13.3])[5].

The RCT of 699 patients for whom SAVR was suitable but high risk (PARTNER 1A, TAVI [n=348] compared with SAVR [n=351]) provides data on haemodynamic properties at 30 days, 6 months and 1 year. At baseline, mean aortic valve area was 0.7 cm^2 (SD 0.2) for TAVI compared with 0.6 cm^2 (SD 0.2) for SAVR (p=0.32). At follow up mean aortic value was significantly higher for TAVI compared with SAVR (1.7 cm^2 (SD 0.5) versus 1.5 cm^2 (SD 0.4) (p=0.001) at 30 days; 1.7 cm^2 (SD 0.5) versus 1.5 cm^2 (SD 0.5) (p=0.01) at 6 months and 1.6 cm^2 (SD 0.5) versus 1.4 cm^2 (SD 0.5) (p=0.002) at 1 year. At baseline, aortic valve gradient values were 42.7 mmHg (SD 14.5) for TAVI compared with 43.5 mmHg (SD 14.3) for SAVR (p=0.51) and the respective figures for 30 days, 6 months and 1 year follow-up were 9.9 mmHg (SD 4.8) versus 10.8 mmHg (SD 5.0) (p=0.04), 10.2 mmHg (SD 4.3) versus 10.8 mmHg (4.8) (p=0.16) and 10.2 mmHg (SD4.3) versus 11.5 mmHg (SD 5.4) (p=0.008). At baseline, LVEF (%) figures were 52.6 (SD 13.5) for TAVI compared with 53.6 (SD 12.5) for SAVR (p=0.35). There were no statistically significant differences in LVEF at follow up for TAVI compared with SAVR (30 days 55.5 [SD 11.4] versus 56.0 [SD 11.4]; p=0.63]; 6 months 56.2 [SD 10.8] versus 56.8 [SD 9.9; p=0.56] and 1 year 56.6 [SD 10.5] versus 57.1 [SD 10.3; p=0.64]). [7; 8; 10].

The other RCT of 795 patients for whom SAVR was suitable but high risk (CoreValve trial, TAVI [n=394] compared with SAVR [n=401] also provides data on haemodynamic properties at baseline, 1 year and 3 years (11; 12).Baseline mean aortic valve area figures were 0.66 cm^2 (SD 0.22) for TAVI compared with 0.67 cm^2 for SAVR (SD 0.25) (not statistically significant) and the respective figures for 1 year were 1.70 cm^2 (SD 0.49) compared with 1.55 cm^2 (SD 0.51) (p<0.001) and for 3 years were 1.79 cm^2 (SD 0.48) compared with 1.53 cm^2 (SD 0.52) (p<0.0001). Baseline figures for mean aortic valve gradient were 49.97 mmHg (SD 14.3) for TAVI and 48.7 mmHg (SD 0.25) for SAVR (not statistically significant). At 1 year the figures were 8.90 mmHg (SD 3.73) for TAVI compared with 12.17 mmHg (SD 7.10) (p<0.0001) and at 3 years follow up they were 7.62 mmHg (SD 3.57) and 11.40 mmHg (SD 6.8) (p<0.0001) respectively. [11; 12].

The RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A)reported larger mean aortic valve area in patients who had TAVI

compared with SAVR at 30 days (1.7 cm^2 [SD 0.5] compared with 1.5 cm^2 [SD 0.4], p<0.001), and this continued at 1 year (1.6 cm^2 [SD 0.4] compared with 1.4 cm^2[SD 0.4], p<0.001) and 2 years (1.5 cm^2 [SD 0.4] compared with 1.4 cm^2 [SD 0.4], p<0.001). There were lower mean aortic valve gradients in patients who had TAVI compared with SAVR at 30 days (9.7 mmHg [SD 3.5] compared with 10.9 mmHg [SD 4.3], p<0.001) and this continued at 1 year (10.7 mmHg [SD 4.5] compared with 11.5 mmHg [SD 4.4], p=0.001) and 2 years (10.8 mmHg [SD 4.6] compared with 11.7 mmHg [SD 4.8], p<0.001). There was a percentage point difference at baseline in average LVEF between patients who had TAVI (56%) and SAVR (55%). At 30 days, the average LVEF was higher for TAVI than SAVR (56.9% [SD 10.2] compared with 55.0% [SD 11.0], p=0.004) but this was reversed at 1 year (55.9% [SD 11.2] compared with 57.2% [SD 9.9], p=0.04) and 2 years (54.9% [SD 11.2] compared with 57.2% [SD 9.7], p=0.005) [(13)].

An RCT of 276 patients for whom SAVR was suitable but intermediate risk (NOTION) reported significant differences in improvements in mean valve area from baseline at 3 months (TAVI 1.7 cm^2 compared with SAVR 1.4 cm^2, p<0.001), 1 year (TAVI 1.7 cm^2 compared with SAVR 1.3 cm^2, p<0.001) and 2 years (SAVR 1.6 cm^2 compared with SAVR 1.3 cm^2, p<0.001) but no significant differences in change from baseline for mean valve gradient [(14)].

Quality of Life

In an RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B) there were significant improvements in in self-reported quality of life in patients in the TAVI group compared with those in the medical management group. On average, those that had TAVI had KCCQ quality-of-life scores that were 14.8 points higher (95% CI 8.6 to 21.0) (p<0.001) at 1 month and the average difference increased at 6 months (24.2 (95% CI 17.4 to 31.6, p<0.001) and 12 months (30.5 (95% CI 22.3 to 38.7, p<0.001) (minimal important difference 5 points, on a scale of 0 to 100, high better)[(4)].

Data were presented for 2 RCTs including patients considered suitable for SAVR but high risk. At 1-month follow-up, patients having TAVI using the transfemoral route reported on average a greater improvement in quality of life when measured using EQ-

5D in both the PARTNER 1A [9] and US CoreValve [18] trials than patients randomised to the SAVR procedure. The PARTNER 1A included 699 patients (348 TAVI; 351 surgical) and reported mean differences from baseline score on EQ5D (where 0 equals dead and 1 perfect health related quality of life) for 192 TAVI patients and 151 SAVR patients. The respective figures were an average change of 0.08 (SD 0.25) for TAVI compared with 0.02 (SD 0.25) for SAVR at 1 month, 0.1 (SD 0.3) compared with 0.09 (SD 0.27) at 6 months and 0.09 (SD 0.23) compared with 0.08 (SD 0.23) at 1 year [9]. The CoreValve trial also provided data on a subset of patients for EQ5D at 1 month, 6 months and 1 year: the average change from baseline at 1 month for TAVI (n=204) was 0.055 (SD 0.23) compared with SAVR (n=144) -0.073 (SD 0.26); at 6 months TAVI (n=221) 0.053 (SD 0.22) compared with SAVR (n=173) 0.04 (SD 0.17) and 1 year TAVI (n=199) 0.043 (SD 0.2) compared with SAVR (n=155) 0.0003 (SD 0.02) [18]. When data from these 2 trials is pooled for the transfemoral route, the overall estimates favoured TAVI significantly at 1 month (RR 0.09 [95% CI 0.03 to 0.16, p=0.006]), however, the differences were not significant at 6 months (RR 0.01 [95% CI -0.02 to 0.05, p=0.47]) and 1 year (RR 0.03 [95% CI 0.00 to 0.06, p=0.09]) [1]. When data was pooled for transapical TAVI compared with SAVR from the PARTNER 1A trial and non-transfemoral TAVI compared with SAVR from the US CoreValve trial, the overall estimates for EQ-5D showed no statistically significant differences between the TAVI and SAVR groups in mean changes from baseline at 1 month (RR -0.03 [95% CI -0.09 to 0.04, p=0.44]), 6 months (RR -0.02 [95% CI -0.10 to 0.06, p=0.64]) and 1 year (RR -0.02 [95% -0.09 to 0.05, p=0.58]) [1].

When comparing the effect of TAVI using transfemoral route with SAVR on SF-12 scores, both the PARTNER 1A[9] and the US CoreValve [18] trials reported a greater improvement on SF-12 in the TAVI than in the SAVR group in both physical and mental scores at 1 month follow-up. Adjusted mean difference for physical summary scores for SF12 were 2.0 (95% CI 0.1 to 3.9, p=0.04) in favour of TAVI at 1 month in PARTNER 1A and 4.9 (95% CI 3.1 to 6.7, p<0.001) in US Core Valve study. The respective figures for mental summary scores were 5.4 (95% CI 3.1 to 7.7, p<0.001) and 6.1 (3.8 to 8.5, p<0.001). At 6 months the only statistically significant difference was reported in the US CoreValve trial [18] using the mental score improvement in the TAVI group compared with the SAVR group (adjusted mean difference of 2.2 (95% CI 0.3 to 4.1, p=0.026). There

were no statistically significant differences between TAVI using either transfemoral or non-transfemoral route and SAVR at 12 months on both physical and mental scores.

Statistically significant differences in favour of TAVI were reported on the KCCQ quality-of-life subscale at 1 month follow-up for patients where the transfemoral access route was used in both PARTNER 1A (adjusted mean difference 9.8 [95%CI 4.0 to 15.6, p=0.001]) and US CoreValve studies (19.0 [95% CI 13.7 to 24.3, p<0.001]) but did not persist to 6 and 12 months follow-up. There were no statistically significant differences in mean change in KCCQ quality-of-life scores for patients who had received TAVI using either transapical route in PARTNER 1A study or non-transfemoral routes in US CoreValve study compared to equivalent patients randomised to SAVR[9; 18].

A systematic review [17] that assessed outcomes at 2 years for patients considered to be at intermediate- and low-risk reported on changes in health related quality of life from baseline using KCCQ score. The review drew on data from 795 patients in 1 study (US Pivotal) with follow-up of 2 years, the mean improvement in score for SAVR patients was 18.7 points and the mean for TAVI was 22.2 points, the mean difference being 3.5 (95% CI 1.9 to 8.9). This finding was not statistically significant and was graded as of low certainty (serious risk of bias and serious imprecision) and therefore might have little or no impact on quality of life.

Repeat hospitalisation

In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B), comparing TAVI (n=179) with medical management (n=179), TAVI had a statistically significantly lower hazard rate of repeat hospitalisation because of aortic stenosis (including complications because of TAVI) than medical management at 2 years (HR 0.41; 95%CI 0.30 to 0.58, p<0.001)[5], 3 years (p<0.0001) [5] and 5 years follow-up p<0.0001).

In the RCT of 699 patients for whom SAVR was suitable but high risk, (PARTNER 1A) there was a non-significant difference in repeat hospitalisation rates (59 [9%] compared with 45 [16%], p=0.38 at 1 year; 74 [25%] compared with 60 [22%], p=0.41 at 2 years; and 108 [42%] compared with 81 [34%], p=0.17 at 5 years) [7; 10]. The RCT of 795 patients (US CoreValve trial, 390 TAVI compared with 357 SAVR as treated) for

whom SAVR was suitable but high risk reported no significant difference in repeat hospitalisation rates (95 [27%] compared with 64 [21.9%], p=0.087) at 3 years. The RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A) reported no significant differences in re-hospitalisation rates between TAVI and SAVR.

An RCT of 699 patients for whom SAVR was suitable but high risk reported comparative figures for repeat hospitalisation at 1, 2 and 5 years. The figures at 1 year were 59 (19%) patients for TAVI compared with 45 (16%) for SAVR (p=0.38); 2 years 74 patients (25%) for TAVI compared with 60 (22%) for SAVR (p=0.41); and 5 years 108 patients (42%) for TAVI compared with 81 (34%) (p=0.17)[7; 10]. An RCT of 390 TAVI patients and 357 SAVR patients for whom surgery was suitable but high risk reported aortic valve hospitalisation in 95 patients (27.%) for TAVI compared with 64 (21.9%) for SAVR (p=0.087) at 3 years[11].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate risk showed no significant differences in rehospitalisation rates between TAVI and SAVR.[13]

Safety

All-cause mortality and cardiovascular mortality within 30 days

An RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B) compared TAVI (n=179) with medical management (n=179). There were no statistically significant differences in all-cause mortality (5% [9/179] compared with 3% [5/179], p=0.41) and cardiovascular mortality (5% [8/179] compared with 2% [3/179], p=0.22) between the TAVI group and medical management at 30-day follow-up[3].

In an RCT of 699 patients for whom SAVR was suitable but high risk (PARTNER 1A, n=348 TAVI compared with =351 SAVR) there were no statistically significant differences in all-cause mortality (3% [12/348] compared with 7% [22/351], p=0.07) and cardiovascular mortality (3% [11/348] compared with 3% [10/351], p=0.90) between the TAVI group and SAVR group at 30-day follow-up) [8]. In another RCT of 795 patients (the

US CoreValve trial, n=394 TAVI compared with n=401 SAVR) there were also no statistically significant differences in all-cause mortality (3% [13/390] compared with 5% [16/357], p=0.43) and cardiovascular mortality (3% [12/390] compared with 5% [16/357], p=0.32) between the TAVI group and SAVR group at 30-day follow-up[12]. When data was pooled for both studies the risk ratio, where less than 1 favours TAVI, for all-cause mortality was 0.64 (95% CI 0.38 to 1.39) (p=0.06) and cardiovascular mortality was 0.90 (95% CI 0.52 to 1.56) (p=0.70)[1].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate or low risk (n=1,011 TAVI compared with n=1,021 SAVR) distinguishes between patients for whom either the transfemoral route (n=773 TAVI; n=775 SAVR) or transthoracic route (n=235 TAVI, n=246 SAVR) is suitable. There was a non-significant lower all-cause mortality (3% compared with 4%, p=0.24) and cardiovascular mortality (2% compared with 3%, p=0.72) for TAVI using the femoral route compared with SAVR at 30-day follow-up. For the transthoracic route the all-cause mortality (6% compared with 4%, p=0.21) and cardiovascular mortality (5% compared with 4%, p=0.47) were not significantly different (13). In another RCT of 280 patients for whom surgery was suitable but low or intermediate risk, (n=145 TAVI compared with n=135 SAVR), all-cause mortality (2% [3/142] compared with 3% [5/134], p=0.43) and cardiovascular mortality (2% [3/142] compared with 4% [5/134], p=0.43) were not significantly different [14]. A systematic review of 6,875 patients for whom surgery was suitable but low to intermediate risk (2 RCTs and 6 observational studies) reported a non-significant lower all-cause mortality rate for TAVI compared with SAVR (odds ratio [OR] 0.67, 95% CI 0.42 to 1.07; p=0.08) at 30-day follow-up.[16]. Another systematic review including 3,179 patients (with risk scores of 8% or less participating in 4 RCTs) also reported a non-significant lower all-cause mortality rate for TAVI compared with SAVR (OR 0.67, 95% CI 0.42 to 1.07)[17].

Cerebral complications

In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B), the hazard ratio of stroke or TIA was significantly higher in the TAVI group (HR 2.81 [95% CI 1.26 to 6.26], p=0.004) at 3-year follow-up [10], whereas at 5-years follow-up there were no significant differences between the treatments (HR 1.39 [95% CI 0.62 to 3.11], p=0.555) [6].

In 2 RCTs (PARTNER 1A [n=699] and US CoreValve [n=795]) with patients for whom SAVR was suitable but high risk, the incidences of stroke and TIA were reported. Both pooled and individual risk ratios from the PARTNER 1A and US CoreValve trials showed no statistically significant differences in all stroke in patients for whom surgery was suitable but high risk at 30-day (RR 1.26, [95% CI 0.56 to 2.83], p=0.57), 1-year (RR 1.21,[95% CI 0.49 to 2.98], p=0.68)), 2-year (RR 1.11, [95% CI 0.51 to 2.41], p=0.78), 3-year (RR 1.14, [95% CI 0.53 to 2.46], p=0.75) and 5-year (PARTNER 1A intention-to-treat RR 1.13, [95% CI 0.68 to 1.87], p=0.65) [(1)]. Both pooled and individual risk ratios for transient ischemic attack from the PARTNER 1A and US CoreValve trials also showed no statistically significant differences at 30-day (RR 3.04, [95% CI 0.62 to 15.01], p=0.017), 1-year (RR 1.46, [95% 0.63 to 3.41], p=0.38), 2-year (RR 1.92,[95% CI 0.90 to 4.11], p=0.09), 3-year (CoreValve ITT RR 1.53,[95% CI 0.55 to 4.25], p=0.42) and 5-year (PARTNER 1A ITT RR 1.77, [95% CI 0.75 to 4.15], p=0.19) [(1; 8; 11; 12; 19)].

In the RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A, TAVI compared with SAVR) there were no significant differences between groups in all strokes at 30 days (TAVI 55 (6%) compared with SAVR 61 (6%), p=0.57), at 1 year (78 (8%) compared with 79 (8%), p=0.88) and at 2 years (91 (10%) compared with 85 (9%), p=0.67)[(13)].

An RCT of 276 patients for whom SAVR was suitable but low to intermediate risk reported incidences of stroke and TIA at 30 days (TAVI 4 (3%) compared with SAVR 4 (3%), p=0.94), at 1 year (TAVI 7 (5%) compared with SAVR 8 (6%), p=0.68) and at 2 years (TAVI 13 (10%) compared with 10 (8%) (p=0.67) [(14)].

A systematic review [(17)] that assessed outcomes at 2 years for patients for whom SAVR was suitable but intermediate- and low- risk found transfemoral-TAVI compared with SAVR was associated with a non-significant reduction in stroke rates in patients considered operable with intermediate and low surgical risk (RR 0.80, 95% CI 0.63 to 1.01). This was based on data from 2,576 patients in 3 studies; and was graded as having moderate uncertainty (serious imprecision). Comparing transapical TAVI with SAVR, the RR was 1.67 (95% CI 0.97 to 2.87). This was based on data from 552 patients in 2 studies and graded as having moderate uncertainty.

Aortic regurgitation

An RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) there were similar rates of moderate or severe aortic regurgitation at 30 days (TAVI 15% compared with standard therapy 17%) and 1 year (15% compared with 17%) [3].

Incidences of aortic regurgitation in patients for whom SAVR was suitable but high risk were reported in the PARTNER 1A and US CoreValve trials, based on patients who had echocardiography study. Moderate or severe aortic regurgitation rates in the PARTNER 1A trial were all statistically significant lower in the SAVR group than in the TAVI group at 30 days (RR 16.29, [95% CI 3.98 to 66.6], p=0.0001)[7], 6 months (RR 30.26, 95% CI 4.16 to 220.01, p=0.0008)(20) and 2 years (p=0.008).I In the US CoreValve trial, moderate or severe aortic regurgitation rates were statistically significantly lower in the SAVR group compared with the TAVI group at 3 years (p=0.04) [11], and in the pooled estimate of the 2 trials at 1 year(pooled RR 4.02, 95% CI 1.99 to 8.11, p=0.0001) [1].

An RCT of 276 patients for whom SAVR was suitable but low to intermediate risk (NOTION, TAVI compared with SAVR) reported significant differences in moderate to severe aortic regurgitation at 3 months (TAVI 15% compared with SAVR 22%, p<0.001) and 1 year (TAVI 16% compared with 1%, p=0.00)1[14].

A systematic review [17] that assessed outcomes at 2 years in patients for whom surgery was suitable but low to intermediate risk found that moderate or severe aortic regurgitation occurred more often at 2 years of follow-up in TAVI than in SAVR patients. This was based on 3 trials, RR=12.22 (95% CI 5.17 to 28.88), with no heterogeneity. This finding was graded as having moderate certainty.

Aortic valve re-intervention

In the systematic review of 3,179 patients for whom SAVR was suitable but intermediate to low risk (based on data from 3,058 patients in 3 studies) the risk for aortic valve re-intervention was significantly higher after TAVI than after SAVR (RR 3.25, 95% CI 1.29 to 8.14).[17].

Prosthesis-patient mismatch

The incidence of prosthesis-patient mismatch in patients for whom SAVR was suitable but high risk was reported in the PARTNER 1A trial [20]. Pibarot et al. (2014) reported the incidence of prosthesis-patient mismatch in the PARTNER 1A trial as 46% (severe 20%) in the TAVI group and 60% (severe 28%) in the SAVR group (p<0.001) assessed at first postoperative echocardiogram, and 42% in the TAVI compared with 57% in the SAVR (p <0.001) at 30 days [21].

Myocardial infarction

There were no significant differences in the occurrence of myocardial infarction (MI) in an RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, comparing TAVI with medical management) at 2 years (p=0.69)[5] and 3 years (p=0.59) follow up[6].

The incidence of MI for patients for whom SAVR was suitable but high risk was reported in the PARTNER 1A trial and the US CoreValve trials. There were no statistically significant differences between the treatment groups in MI in either the pooled estimate at 30 day follow-up (RR 0.72 [95% 0.147 to 2.94] (p=0.64), 1 year (RR 1.18 [95% CI 0.42 to 3.29]; p=0.76) or 2 year (RR 0.51 [95% CI 0.06 to 4.05]; p=0.52), or the finding reported in the single studies at the 3 year (US Core Valve intention-to-treat RR 1.45 [95% CI 0.45 to 2.94; p=0.52) or 5 year (PARTNER 1A intention-to-treat RR 0.46 [95% CI 0.16 to 1.31]; p=0.14) follow-up, based on intention-to-treat analysis[1].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate risk reported no significant differences in incidences of MI between TAVI and SAVR [13].

An RCT of 276 patients for whom SAVR was suitable but low to intermediate risk reported no significant differences in MI between TAVI and SAVR [14].

A systematic review that assessed outcomes at 2 years for patients for whom SAVR was suitable but intermediate- and low- risk found no effect on MI (RR 0.87, 95% CI 0.59 to 1.29) at 2 year follow up based on data from 3,128 patients in 4 studies. The certainty of this finding was graded as moderate[17].

Endocarditis

In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, comparing TAVI with medical management) there were no significant differences in the occurrence of endocarditis between TAVI and those who received standard care at 2 years (2% compared with 1%, p=0.32) and 3 years (2% compared with 1%, p=0.32) [5; 6].

In an RCT of 699 patients for whom SAVR was suitable but high risk (n=348 TAVI, n=351 SAVR) there was no significant difference in the occurrence of endocarditis at 1 month (TAVI 0% compared with SAVR 1 [<1%], p=0.32), 1 year (TAVI 2 [1%] compared with 3 [1%], p=0.63), 2 years (TAVI 4 [2%] versus 3 [1%], p=0.61) and 5 years (TAVI 5 [2%] compared with 6 [3%], p=0.65) [7; 8; 10] . Another RCT of 795 patients for whom surgery was suitable but high risk (n=394 TAVI, n=401 SAVR) reported 3 cases (1%) in TAVI group compared with 5 cases (2%) in SAVR group (p=0.346) at 3 years [11].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (n=1,011 TAVI, n=775 SAVR) reported no cases of endocarditis at 1 month in any study arm. The study reports incidences separately for patients for whom transfemoral TAVI or transthoracic TAVI was suitable. For those for whom transfemoral TAVI was suitable, the incidences at 1 year were 6 (1%) for TAVI compared with 6 (1%) for SAVR (p=0.92) and at 2 years 10 (2%) compared with 6 (1%) (p=0.33). For those for whom transthoracic TAVI was suitable, there was 1 case in the TAVI arm compared with no cases in the SAVR arm (p=0.32) reported at both 1 and 2 years follow up [13].

An RCT of 276 patients (n=142 TAVI, n=134 SAVR) for whom SAVR was suitable but low to intermediate risk reported incidences of valve endocarditis at 30 days (TAVI 1 [1%] compared with SAVR 0, p=0.33) and 1 year (TAVI 4 [3%] compared with 2 [2%], p=0.47) [14].

Atrial fibrillation

An RCT of 358 patients for whom SAVR was unsuitable (n=179 TAVI, n=179 standard therapy) reported incidences of new atrial fibrillation at 30 days (TAVI less than1%

compared with standard therapy 1%, p=1.00) and 1 year (less than 1% compared with 2%, p=0.62) [3].

An RCT of 699 patients for whom SAVR was suitable but high risk reported that 12% of the TAVI group had new atrial fibrillation compared with 17% of SAVR group (p=0.07)[8] at 1-year follow up. Another RCT of 795 patients for whom surgery was suitable but high risk reported 45 new cases (12%) in the TAVI group compared with 108 (31%) in the SAVR group (p<0.001) at 30-days follow up and 60 new or worsening cases (15%) in the TAVI group compared with 115 (33%) in SAVR group (p<0.001) at 1-year follow up [12].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate risk reported new atrial fibrillation separately for those considered appropriate for transfemoral and transthoracic TAVI. For those for whom transfemoral TAVI was suitable, the incidence of new atrial fibrillation was: TAVI, 38 [5%] compared with SAVR 204 [27%], p<0.001 at 30 days, TAVI 45 [6%] compared with SAVR 210 [28%], p<0.001 at 1-year and TAVI 55 [7%] compared with SAVR 211 [28%] p<0.001 at 2-years. The respective figures for those for whom transthoracic TAVI was suitable were: TAVI 53 [23%] compared with SAVR 61 [25%], p=0.50 at 30-days, TAVI 55 [24%] compared with SAVR 62 [26%], p=0.60 at 1-year and TAVI 55 [24%] compared with SAVR 62 [26%], p=0.60 at 2-years [13].

An RCT of 276 patients for whom SAVR was suitable but low to intermediate risk reported cases of new onset or worsening atrial fibrillation at 30 days (TAVI, 24 [17%] compared with SAVR, 77 [58%], p<0.001), 1 year (TAVI, 30 [21%] compared with 79 [60%] p<0.001) and 2 years (TAVI 32 [23%] compared with SAVR 80 [60%] (p<0.001) [14].

A systematic review (19) that assessed outcomes for patients for whom SAVR was suitable but low to intermediate risk found that the relative risk for new onset atrial fibrillation at 2 years follow up was 0.43 (95% CI 0.35 to 0.52) for TAVI compared with SAVR. This was based on data from 3,058 patients in 3 studies and had a high degree of certainty.

Need for permanent pacemaker

In an RCT of 358 patients for whom SAVR was unsuitable (n=179 TAVI, n=179 standard therapy), the proportion of patients with permanent pacemaker implantation was lower in the TAVI group at 2-years (6% compared with 9%, p=0.47) [5] although no significant differences were observed at 3-years (8% compared with 9%, p=0.75) [6].

When data is pooled for the 2 RCTs comparing TAVI (n=742) against SAVR (n=752) in patients for whom SAVR was suitable but high risk, the estimates for needing new permanent pacemaker implantation all tended to favour the SAVR group, however the differences were not statistically significant: 30 days (RR 1.94 [95% CI 0.70 to 5.34], p=0.20), 1 year (RR 1.75 [95% CI 0.94 to 3.25], p=0.08) and 2 years (RR 1.77 [95% CI 0.95 to 3.30], p=0.07) [1]. Follow up data was available for 3 years for the US CoreValve trial (n=394 TAVI, n=401 SAVR).There were statistically fewer permanent pacemaker implantations reported in the SAVR group (14.5%) than TAVI group (28%) (p<0.001) [11]. In PARTNER 1A there was no statistically significantly difference between the 2 treatment groups (TAVI 9.7% versus SAVR 9.1%, p=0.64) at 5 years [7].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate risk reported new pacemakers in 9% of TAVI patients compared with 7% SAVR (p=0.17) at 30 days and 10% compared with 9% (p=0.43) at 1 year and 12% compared with 10% (p=0.29) at 2 years [13].

An RCT of 276 patients for whom SAVR was suitable but low to intermediate risk reported higher incidences of the need for new pacemakers in the TAVI group than SAVR group at 30 days (TAVI 46 [34%] compared with SAVR 2 [2%], p<0.001), at 1 year (TAVI 51 [38%] compared with SAVR 3 [2%], p<0.001) and 2 years (TAVI 55 [41%] compared with SAVR 5 [04%], p<0.001) [14].

A systematic review that assessed outcomes at 2 years for patients for whom SAVR was suitable but intermediate and low risk found an increased risk of permanent pacemaker implantation (RR 2.46, 95%CI 1.17 to 5.15) based on data from 3,128 patients in 4 studies; at a follow-up of 2 years. This finding was graded as having high certainty despite heterogeneity [17].

Acute kidney injury and renal failure

In an RCT of 358 patients for whom SAVR was unsuitable (n=179 TAVI, n=179 standard therapy) there were no significant differences in the occurrence of acute kidney injury (AKI) between those who received TAVI and standard care at 2 years (3% for TAVI compared with 8% for SAVR p=0.15) [(5)] and 3 years (3% for TAVI compared with 11% for SAVR, p=0.08) follow up [(6)].

Both the PARTNER 1A and the US CoreValve trials reported on AKI comparing TAVI with SAVR in patients for whom SAVR was suitable but high risk. Based on intention-to-treat analysis, both the pooled risk ratio at 30-day and the risk ratio from the individual US CoreValve study at 3 years significantly favoured the TAVI group; whereas there were no statistically significant differences in the pooled estimates at 1 year and 2 years and from the individual PARTNER 1A trial at 5 years [(1)]. Pooled estimates were RR 0.51 (95% CI 0.27to 0.98) p=0.04 at 30 days; RR 0.76 (95% CI 0.23 to 2.59) at 1 year; RR 0.64 (95% CI 0.31 to1.34), p=0.24 at 2 years [(1)]; and individual studies RR 0.45 (95% CI 0.29 to 0.72) p=0.0007 at 3 years [(11)] and RR 1.01 (95% CI 0.58 to 1.74) [(7)].

An RCT of 2,032 patients for whom SAVR was suitable but intermediate risk reported a lower incidence of AKI amongst TAVI patients than SAVR patients at 30 days (13 [1.3%] compared with 31 [3%], p=0.0006). Incidence rates were similar for transthoracic TAVI and SAVR (4% compared with 3%). At 1 year the incidence rates were lower for transfemoral TAVI (2.2%) than control SAVR (5%) (p=0.002) and higher for transthoracic TAVI (7%) than control SAVR (4.4%) (p=0.18). At 2 years the respective figures were 3% compared with 7% (p<0.001) and 8% compared with 6% (p=0.23)[(13)].

An RCT of 276 patients for whom SAVR was suitable but low to intermediate surgical risk reported a higher occurrence of acute kidney injury in SAVR (9 cases [7%]) than TAVI (1 case [0.7%]) at 30 days (p=0.01) [(14)].

A systematic review [(17)] that assessed outcomes at 2 years for patients for whom SAVR was suitable but intermediate or low risk found that for transfemoral TAVI compared with SAVR, the relative risk of AKI was 0.38 (95% CI 0.27 to 0.54) at 2 years, based on data from 2,576 patients in 3 studies; for transapical TAVI, the relative risk was 1.54 (95% CI

0.77 to 3.07). The certainty of this finding in transfemoral TAVI was graded as high but was graded as low for transapical TAVI.

Vascular complications

In an RCT of 358 patients for whom SAVR was unsuitable (n=179 TAVI, n=179 standard therapy) the hazard ratio [HR] for major vascular complications at 3-years follow-up was statistically significantly higher in the TAVI group than those in standard care (HR 8.27, 95% CI 2.92 to 23.44, p<0.0001)[6].

Major vascular complications were reported for patients for whom SAVR was suitable but high risk in the PARTNER 1A trial and the US CoreValve trial. Although the SAVR group tended to have a lower risk rate at all the follow-up points, there were no statistically significant differences between the treatments in either pooled estimates at 30 day (p=0.17), 1 year (p=0.38) or 2 year (p=0.09) follow-up[1], or in the individual studies at 3 year (US CoreValve study p=0.42)[11] or 5 year (PARTNER 1A p=0.19)[7] follow-up.

The RCT of 2,032 patients for whom SVAR was suitable but intermediate risk reported a higher overall incidence of major complications in the TAVI group than the SAVR group (7.9% compared with 5%, p=0.008 at 30 days, 8% compared with 5.3%, p=0.007 at 1 year and 9% compared with 6%, p=0.006 at 2 years). There were differences between patients for whom transfemoral and transthoracic TAVI were suitable: the incidence rate was lower, but not statistically significant, in those that had transthoracic TAVI than matched SAVR patients[13].

The RCT of 276 patients for whom SVAR was suitable but low to intermediate surgical risk reported higher prevalence of major vascular complications in patients having TAVI than SAVR (6% compared with 2%,p=0.10) [15].

Major bleeding inoperable patients

In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management), the risk of major bleeding was statistically significantly higher for TAVI than medical management (29% compared with 20%,

p=0.04) at 2 years[5], but not statistically significant different (32% compared with 33%, p=0.92) at 3-years follow-up [6] .

In 2 RCTs (PARTNER 1A [n=699] and US CoreValve [n=795], comparing TAVI with SAVR) of patients for whom SAVR was suitable but high risk, there was no statistically significant differences between the treatment groups in the risk of major bleeding in either pooled data at 30-day (RR 0.67, 95% CI 0.36 to 1.25, p=0.21), 1-year (RR 0.73, 95% CI 0.48 to1.12 p=0.15) and 2-year follow-up (RR 0.78, 95% CI 0.54 to1.13, p=0.19)[1] or in the individual study at 3-year (RR 0.92, 95% CI 0.75 to 1.12, p=0.38) follow-up. However, it was significantly lower in the TAVI group than SAVR in the individual study at 5-year follow-up (RR 0.73, 95% CI 0.57 to 0.95, p=0.02)[7].

In 2 RCTs (PARTNER 2A and NOTION, comparing TAVI with SAVR) in 2,032 and 276 patients, for whom SAVR was suitable but intermediate risk, the risk of major bleeding was reported. The RCT of 2,032 patients reported significantly lower incidence of life threatening or disabling bleeding in patients that had TAVI than SAVR at 30 days (10%, [105/1011] compared with 43% [442/1021], p<0.001), 1 year (15% [151] compared with 46% [460]) and 2 years follow-up (17% [169] compared with 47% [471], p<0.001). The rates were also significantly lower in patients who had transthoracic TAVI rather than SAVR (23% compared with 50%, p<0.001 at 30 days, 29% compared with 52%, p<0.001 at 1 year and 30% compared with 54%, p<0.001 at 2 years follow-up). [13]. The RCT of 276 patients reported significantly lower incidence of bleeding in the TAVI group than the SAVR group at 30 days (11% [16] compared with 21% [28], p=0.03)[14].

A systematic review that assessed outcomes at 2 years for patients considered to be at intermediate and low surgical risk found transfemoral TAVI was associated with a large significant reduction in life threatening or disabling bleeding or major bleeding (RR 0.39, 95% CI 0.29 to 0.54). This was based on data from 2,576 patients in 3 studies and the finding was graded as having high certainty. Compared to SAVR, transapical TAVI also had a reduced risk of life threatening or disabling bleeding or major bleeding , RR 0.53 (95% CI 0.42 to 0.67) based on data from 552 patients in 2 studies; also graded as high certainty[17].

Rare safety events

A number of observational studies (listed in table A2) reported rare safety events associated with TAVI for severe aortic stenosis including: acute myocardial infarction, acute myocardial injury from damage to apical epicardial collateral circulation, acute occlusion of right coronary artery, acute severe occlusion of the left main coronary artery, aortic arch rupture, aortic dissection, aorta perforation, aortic rupture (abdominal), aorto-right ventricular defect (lethal), apical left ventricular thrombus, apical tear, balloon rupture, catheter-induced ventricular septum defect, circumflex artery occlusion, cutaneo-pericardial fistula, delayed ventricular apical bleed, distal coronary embolisation, early valve degeneration, elliptic distortion of the aortic prosthesis, false left ventricular apical aneurysm, guide wire thrombus formation, iatrogenic chordal rupture, iliac artery rupture, intercostal artery pseudoaneurysm, interventricular septum rupture, late prosthesis migration and rotation, left ventricular pseudoaneurysm, major bleeding from the apex, mitral valve destruction by wire entrapment, multivessel coronary artery spasm, papillary muscle rupture, perforation of the medial circumflex branch of the common femoral artery, pseudoaneurysm at the left ventricular apical access site, pseudoaneurysm of the apex, ruptured pseudoaneurysm of a renal artery, Takotsubo syndrome and valve embolisation.

Validity and generalisability of the studies

In all risk groups, RCT evidence on the efficacy of TAVI was available. Given the nature of TAVI and its comparators, blinding of investigators and patients was not possible. There were insufficient studies for formal assessment of publication bias.

Patients in the RCTs were followed for at most up to 5 years, hence there is some uncertainty about longer term outcomes of TAVI. Patients who are candidates for TAVI however have a poor prognosis and RCT populations had a high mean age, so competing risks of death will become more prominent should longer term follow-up data become available.

Although there was some RCT evidence on TAVI using the transfemoral route and less on the transapical route, greater precision on outcomes using specific routes in different risk populations would be desirable. Likewise, greater precision in the quantification of

some safety outcomes would facilitate the characterisation of the risk and benefit profiles of SAVR and TAVI.

There is some uncertainty around the risk stratification of studies, given that RCTs have overlapping patient populations to a certain degree. This particularly applies to the US CoreValve trial which, given the inclusion criteria and baseline patient characteristics, has been included within our review in the high-risk group but also in 2 systematic reviews of intermediate and low-risk patient populations. This problem cannot be addressed in study level meta-analysis. Individual patient data meta-analysis, should trial sponsors agree to release data, would be needed to more fully explore the effectiveness and safety of TAVI based on risk stratification.

Existing assessments of this procedure

The 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement sets out indications for patients with aortic stenosis where SAVR, TAVI, Balloon Aortic Valvuloplasty and medical therapy may be most appropriate. TAVI is recommended in patients with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVI and a predicted survival of more than 12 months, and who have a prohibitive surgical risk as defined by an estimated 50% or greater risk of mortality or irreversible morbidity at 30 days, or other factors such as frailty, prior radiation therapy, porcelain aorta, and severe hepatic or pulmonary disease. The consensus statement also provided recommendations on suitable sites, development of centre and physician expertise, post procedural care and data that should be recorded in registers[22].

The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) published revised guidelines on the management of valvular heart disease in 2012 including specific guidance on the use of TAVI for patients with aortic stenosis: TAVI should only be performed in hospitals with cardiac surgery on-site. A ‘heart team’ that assesses individual patient’s risks, as well as the technical suitability of TAVI and access issues, should be best able to make decisions in this patient population. Contraindications, both clinical and anatomical, should be identified. Eligible patients

should have a life expectancy of more than 1 year and should also be likely to gain improvement in their quality of life, taking into account their comorbidities. Based on current data, TAVI is recommended in patients with severe symptomatic aortic stenosis who are, according to the 'heart team', considered unsuitable for conventional surgery because of severe comorbidities. Among high-risk patients who are still candidates for surgery, the decision should be individualised. TAVI should be considered as an alternative to surgery in those patients for whom the 'heart team' favours TAVI, taking into consideration the respective advantages/disadvantages of both techniques. A logistic Euro-SCORE ≥20% has been suggested as an indication for TAVI therapy but EuroSCORE is known to markedly overestimate operative mortality. In the absence of a perfect quantitative score, the risk assessment should mostly rely on the clinical judgement of the 'heart team', in addition to the combination of scores. At the present stage, TAVI should not be performed in patients at intermediate risk for surgery and trials are needed in this population[23].

The Valve Academic Research Consortium published a revised set of end point definitions and consensus recommendations for implementation in TAVI clinical research programmes in 2012. These included the following safety and efficacy end points: mortality, myocardial infarction, stroke, bleeding complications, acute kidney injury, conduction disturbances and arrhythmias, valvular function, transcatheter valve stenosis, transcatheter valve regurgitation and quality of life. The revised guidance provided end point definitions for a number of TAVI related complications not provided in the previous version including conversion to open surgery, unplanned use of cardiopulmonary bypass, coronary obstruction, ventricular septal perforation, cardiac tamponade, endocarditis, valve thrombosis, valve malpositioning and TAV-in-TAV deployment [24].

Health Improvement Scotland published Advice Statements on whether TAVI was clinically and cost effective for severe symptomatic aortic stenosis in adults not eligible for surgery (Advice Statement 001/14) and in adults at high surgical risk (Advice Statement 002/14) along with supporting evidence notes. The first note concluded 'Despite remaining uncertainty over cost effectiveness and the safety issues associated with the use of TAVI in patients ineligible for surgery, the evidence of clinical benefits supports the use of TAVI for inoperable patients and the ongoing collection of patient selection and outcome data. TAVI technology continues to evolve.' The second note

concluded: ‘The evidence reviewed indicated that TAVI and surgical AVR provide similar clinical benefits to patients at high surgical risk but there was an increase in adverse events with TAVI. Cost effectiveness has not been adequately demonstrated. The evidence reviewed does not support the provision of TAVI for AS in adults at high surgical risk.’ Both advice notes refer to ‘Rapid progress is being made in device modification and patient selection such that the published evidence base may not fully capture the emergent evidence for the latest generation of TAVI devices.’

A HTA commissioned by NIHR published in 2013 concluded for patients unsuitable for surgical aortic valve replacement (SAVR), transcatheter aortic valve implantation (TAVI) is likely to be cost effective compared with medical management; however, for SAVR-suitable patients TAVI could be more costly and less effective, and the cost-effectiveness of TAVI is likely to depend on a very substantial majority of patients being unsuitable for SAVR [(25)].

Health Quality Ontario published a HTA in 2016 that identified and analysed randomised controlled trials that evaluated the effectiveness and safety of TAVI compared with SAVR or balloon aortic valvuloplasty and were published before September 2015. This study concluded that ‘moderate quality evidence showed that TAVI and SAVR had similar mortality rates in patients who were eligible for surgery. Information about quality of life showed similar results for TAVI and SAVR in the first year, but was based on low quality evidence. Moderate quality evidence also showed that TAVI was associated with higher rates of adverse events than SAVR. In patients who were not suitable candidates for surgery, moderate quality evidence showed that TAVI improved survival compared with balloon aortic valvuloplasty. When TAVI was compared with SAVR, the incremental cost-effectiveness ratio was Canadian $51,988 per quality-adjusted life-year.’[(26)]

Based on data from a systematic review (study 7 above), BMJ Rapid Recommendations has published a clinical guideline on transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk, available as an app.

The American College of Cardiology Taskforce on Clinical Consensus Document has prepared a decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis (in press)[27].

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

- Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. NICE interventional procedure guidance IPG 541. (2015). Available from https://www.nice.org.uk/guidance/ipg541
- Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction. NICE interventional procedure guidance IPG 504 (2014). Available from https://www.nice.org.uk/guidance/ipg504
- Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. NICE interventional procedure guidance IPG 436 (2013). Available from https://www.nice.org.uk/guidance/ipg436
- Sutureless aortic valve replacement for aortic stenosis. NICE interventional procedure guidance IPG 456 (2013). Available from https://www.nice.org.uk/guidance/ipg456
- Transcatheter aortic valve implantation for aortic stenosis. NICE interventional procedure guidance IPG 421 (2012). This guidance is currently under review and is expected to be updated in 2017. For more information see https://www.nice.org.uk/guidance/ipg421
- Percutaneous fetal balloon valvuloplasty for aortic stenosis. NICE interventional procedure guidance IPG 175 (2006). Available from https://www.nice.org.uk/guidance/ipg175
- Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE interventional procedure guidance IPG 78 (2004). Available from https://www.nice.org.uk/guidance/ipg78

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by

Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Advisor Questionnaires for transcatheter aortic valve implantation for aortic stenosis were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires these will be discussed by the committee.

Company engagement

A structured information request was sent to 7 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. These were considered by the NICE external assessment centre and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

In accordance with NICE guidelines this review does not include grey literature such as conference presentations. The review team did, however, check conference abstracts where appropriate to identify rare safety events at the request of the interventional procedures team.

The evidence did not include subgroup analyses comparing TAVI valves from different manufacturers. Moreover, these devices and delivery systems are subject to incremental innovation and newer valve devices are now marketed. The UK TAVI register collects information on the device manufacturer and might be a future source of information.

The following ongoing studies were identified:

Comparisons of TAVI with SAVR or standard practice

Trial ID	Official title	Expected completion date	Status	Valve and route	Brief description
ISRCTN57819173	The United Kingdom Transcatheter Aortic Valve Implantation (UK TAVI) Trial. A multi-centre randomised controlled trial to assess the clinical effectiveness and cost utility of TAVI, compared with conventional surgical aortic valve replacement (AVR), in patients with severe symptomatic aortic stenosis at intermediate or high operative risk	Expected to run until July 2016	Completed	Any commercially available device	RCT Non-inferiority of TAVI versus SAVR in patients at intermediate or high operative risk over a 5-year period.
NCT01586910	Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI). (SURTAVI)	October 2016 (final collection date for primary outcome)	Recruiting	Self-Expanding Medtronic CoreValve	RCT TAVI vs SAVR in patients with severe AS at intermediate surgical risk
NCT02675114	A Prospective, Randomized, Controlled, Multi-Center Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients Requiring Aortic Valve Replacement Who Have Severe, Calcific, Symptomatic Aortic Stenosis (PARTNER 3)	March 2027	Recruiting	Sapien 3 Transcatheter Heart Valve and Edwards Commander Delivery System	RCT TAVI vs SAVR Low risk patients (<2% operative mortality risk)
NCT02701283	Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement	March 2023	Recruiting	Medtronic CoreValve System TAVI device or the Medtronic Corevalve Evolut R System Transcatheter Aortic Valve Implantation (TAVI)	RCT: TAVI vs SAVR in subjects who have a low predicted risk of operative mortality for SAVR with a commercially approved surgical bioprothesis
NCT02825134	Nordic Aortic Valve Intervention Trial 2 - A Randomized Multicenter Comparison of Transcatheter Versus Surgical Aortic Valve Replacement in Younger Low Surgical Risk Patients With Severe Aortic Stenosis (Notion-2)	June 2024	Not yet recruiting	Retrograde transfemoral transcatheter aortic valve replacement with any CE mark approved aortic bioprosthesis with or without concomitant percutaneous coronary intervention.	TAVI vs SAVR Low risk for conventional surgery (STS Score <4%) aged 18-75 years
NCT02661451	Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure: A Randomized Trial (TAVR UNLOAD)	March 2018 (final data collection date for primary	recruiting	SAPIEN 3 THV via a transfemoral approach	RCT: TAVR in heart failure patients with moderate aortic valve stenosis as compared with optimum heart failure treatment

Trial ID	Official title	Expected completion date	Status	Valve and route	Brief description
		outcome measure)			
TAVI cohorts					
NCT01675596	The SOLACE-AU Clinical Trial. A Multicentre, Non-Randomised Controlled Study of the Safety, Performance, Quality of Life and Cost Effectiveness Outcomes of the Edwards SAPIEN XT™ Transcatheter Heart Valve in an Australian Population	2018	Recruiting	Edwards SAPIEN XT™ valve with the NovaFlex delivery system	Cohort TAVI outcomes. Outcomes to be compared to SAVR patients in cohort A of the PARTNER II trial
NCT02838199	TRANscatheter or SurgIcal Aortic Valve ReplacemenT in All-Comers With Severe Not yet open Aortic Valve Stenosis (TRANSIT)	December 2020	Not yet recruiting	Edwards Sapien3	RCT: To determine superiority of TAVI to SAVR with bio-prosthesis
NCT02711540	Retrospective Analysis of Procedural Aspects of Transcatheter Aortic Valve Implantation (TAVI) on periprocedural stroke rates in the United Kingdom	July 2016 (final date for primary outcome measure)	Active, not recruiting	All patients who had TAVI in the UK	Retrospective cohort analysis of all TAVI patients in the UK for stroke predictors
NCT02404467	Feasibility And Safety of Early Discharge After Transfemoral Transcatheter Aortic Valve Implantation The FAST-TAVI Study	March 2017	Recruiting	Valve type unspecified TF-TAVI	Prospective observational. Evaluation of whether patients considered high or intermediate risk for surgery, but relatively low risk for TAVI, can be discharged early after the procedure (within the first 2-3 days) without additional risks.
NCT02695147	Direct Aortic vs Subclavian Access for TAVI: a Review of the Outcomes in the UK	June 2016 (Final data collection date for primary outcome measure)	Ongoing but not recruiting patients	Any TAVI procedure using any valve type performed via the subclavian approach Vs Any TAVI procedure using any valve type performed via the direct aortic approach	Retrospective cohort study
Comparisons of different types of TAVI					
NCT02737150	SecOnd-generation seLf-expandable Versus Balloon-expandable Valves and gEneral Versus Local Anesthesia in TAVI (SOLVE-TAV)	April 2021	Recruiting	CoreValve Evolut R self-expandable valve Edwards Sapien 3 balloon valve	RCT to demonstrate equivalence of second-generation self-expandable valves (CoreValve Evolut R) in comparison to second-generation balloon-expandable valves (Edwards Sapien 3) and of local anesthesia with conscious sedation in comparison to

Trial ID	Official title	Expected completion date	Status	Valve and route	Brief description
					general anesthesia with respect to safety and efficacy in high-risk patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. RCT with 4 arms: Core Valve and Balloon valve each 1. under local anesthesia with conscious sedation 2. under general anesthesia STS risk score ≥10% and/or high risk/contraindication to conventional surgical aortic valve replacement
NCT02163850	SALUS Trial TranScatheter Aortic Valve RepLacement System Pivotal Trial The Safety and Effectiveness of the Direct Flow Medical Tanscatheter Aortic Valve System	December 2021	Recruiting	Direct Flow Medical	RCT of TAVI with Direct Flow vs Medtronic CoreValve or Edwards Sapien In in high and extreme risk patients were severe AS
NCT02000115	Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial	June 2018 (final data collection date for primary outcome measure)	Recruiting	St Judes Medical Portico via transfemoral and alternative delivery methods	RCT of St Judes Portico system vs “Commercially available transcatheter aortic valve” A high risk cohort and extreme risk cohorts.
NCT02202434	REPRISE III: Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System - Randomized Clinical Evaluation	January 2017 (final data collection date for primary outcome measure)	recruiting	Lotus™ Valve System	RCT TAVI with Lotus system vs TAVI with CoreValve system in subjects with calcific AS, who are considered at extreme or high risk for surgical valve replacement.

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Appendix A: Additional papers on transcatheter aortic valve implantation

We first set out studies reported in supporting systematic review but not included in this overview. Then list other studies excluded from the systematic review. The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction tables (table 2-8). It is by no means an exhaustive list of potentially relevant studies.

Table A1: Papers included in supporting systematic review but not the overview

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Arora S, Misenheimer JA, Jones W, et al. (2016). Transcatheter versus surgical aortic valve replacement in intermediate risk patients: a meta-analysis. Cardiovasc Diagn Ther;6:241-9.	Systematic Review	In intermediate risk patients undergoing aortic valve replacement, the risk of mortality, neurological outcomes, and MI do not appear to be significantly different between TAVR and SAVR. There appears to be a significant reduction in risk of acute renal failure at and increased risk of requiring a permanent pacemaker in low and intermediate risk patients undergoing TAVR compared to SAVR	Not as high quality as Gargiulo et al 2016 and Siemieniuk et al 2016 reviews
D'Onofrio A, Messina A, Lorusso R, et al (2012). Sutureless aortic valve replacement as an alternative treatment for patients belonging to the "gray zone" between transcatheter aortic valve implantation and conventional surgery: a propensity-matched, multicenter analysis. J Thorac Cardiovasc Surg;144:1010-6	468 females in TA-TAVI propensity-matched study	No statistically significant difference was found in hospital mortality in high-risk operable women.	Matched comparison study not RCT
Elmariah S, Palacios IF, McAndrew T, et al.(2013). Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort A). Circ Cardiovasc Interv;6:604-14	699. Stratified by the presence of left ventricular ejection fraction <50%	In high-risk patients with severe aortic stenosis and left ventricular (LV) dysfunction, mortality rates and LV functional recovery were comparable.	Exploratory analysis of a subgroup of PARTNER 1A participants.
Greason KL, Mathew V, Suri RM, et al. (2014) Transcatheter versus surgical aortic valve replacement in patients with prior coronary artery bypass graft operation: a PARTNER trial subgroup analysis. Ann Thorac Surg;98:1-7.	288 with a history of CABG	In patients who previously had a CABG no statistically significant differences in NYHA classification were found between TAVI and SAVR groups at 30 days, 6 months, 12 and 24 months follow-up points.	Exploratory analysis of a subgroup of PARTNER 1A participants
Higgins J, Ye J, Humphries KH, , et al (2011).. Early clinical outcomes after transapical aortic valve implantation: a propensity-matched comparison with conventional aortic valve replacement. J Thorac Cardiovasc Surg 142:e47-52.	46 in TAVI and 46 in SAVR	Among high-risk propensity-matched patients, early clinical outcomes are similar after transapical aortic valve implantation and conventional aortic valve replacement.	Matched comparison study not RCT
Khan AR, Khan S, Riaz H, , et al.(2016). Efficacy and safety of transcatheter aortic valve replacement in intermediate surgical risk patients: A systematic review and meta-analysis. Catheter Cardiovasc Interv; Epub ahead of print.	Systematic Review included 1 RCT and 6 observational studies with intermediate risk patients.	Found no evidence of effect on mortality at 30 days or 1 year.	Not as high quality as Gargiulo et al 2016 and Siemieniuk et al 2016 reviews
Lindman BR, Pibarot P, Arnold SV, et al. (2014).Transcatheter versus surgical aortic valve replacement in patients with diabetes and severe aortic stenosis at high risk for surgery: an analysis of the PARTNER Trial (Placement of Aortic Transcatheter Valve). J Am Coll Cardiol ;63:1090-9.	275 with diabetes of those underwent treatment in the PARTNER 1A trial	No statistically significant differences were found between the treatments for all-cause mortality except at 1 year where the results favoured the TAVI group (HR 0.60, 95% CI 0.36 to 0.99, p=0.04). At both discharge and 6 months there were significantly lower proportion of patients in NYHA class III/IV in the TAVI than in the SAVR group, whereas no significant differences were observed at both 1 year and 2 years.	Exploratory analysis of a subgroup of PARTNER 1A participants

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Nielsen HH, Klaaborg KE, Nissen H, et al. (2012) .A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. EuroIntervention **8**:383-9	Randomised: 72 TAVI (n=34) vs SAVR (n=36)	Given the limitations of a small prematurely terminated study, the authors suggest that a-TAVI in its present form may be associated with complications and device success rates in low-risk patients similar or even inferior to those found in high-risk patients with aortic valve stenosis.	Small RCT which was terminated early before reaching target of 200
Onorati F, D'Errigo P, Barbanti M, et al. (2013). Results differ between transaortic and open surgical aortic valve replacement in women. Ann Thorac Surg;96:1336-42.	Females, 194 in TAVI and 194 in SAVR propensity-matched study	No statistically significant difference was found in hospital mortality in high-risk operable women.	Matched comparison study not RCT
Skelding KA, Yakubov SJ, Kleiman NS, et al. (2016) Transcatheter Aortic Valve Replacement Versus Surgery in Women at High Risk for Surgical Aortic Valve Replacement (from the CoreValve US High Risk Pivotal Trial). Am J Cardiol;118:560-6.	353 women of randomised to Core Valve study	No statistically significant differences were observed between the two treatment groups at 30 days and 1 year in the proportion of patients with NYHA class I, II, III and IV in high-risk operable women in the US CoreValve trial.	Exploratory analysis of a subgroup of CoreValve participants
Zorn GL 3rd, Little SH, Tadros P, et al. (2016). Prosthesis-patient mismatch in high-risk patients with severe aortic stenosis: A randomized trial of a self-expanding prosthesis. J Thorac Cardiovasc Surg;**151**:1014-22		Zorn et al. (2016) reported the proportions of patients in different NYHA classifications at 1, 6 and 12 months respectively in patients who had a prosthesis-patient mismatch (PPM) in the CoreValve trial. In those who had non-severe PPM there were significantly higher proportion of patients with NYHA III or IV at 1 month, 6 months and 1 year; whereas the differences were insignificant at any of these follow-ups in those with severe PPM	Exploratory analysis of a subgroup of CoreValve participants

Observational studies reporting rare safety events

Safety event	Study
Acute myocardial infarction	Wendler O, et al. The JUPITER registry: Thirty-day primary endpoint Results of a second generation transapical TAVI system. EuroIntervention. Conference: EuroPCR 2014. Zhao QM, et al. Procedural Results and 30-day clinical events analysis following Edwards transcatheter aortic valve implantation in 48 consecutive patients: initial experience. Chinese Medical Journal 2012;**125**:2807-2810.
Acute myocardial injury from damage to apical epicardial collateral circulation	Khan ZA, et al. When we should say no to TAVR-Defining the line between utility and futility. Cardiovasc Revasc Med 2016;**17**:424-7.
Acute occlusion of right coronary artery	Wolf A, et al. Successful repositioning of a direct flow medical 25-mm valve due to acute occlusion of right coronary artery during transcatheter aortic valve replacement procedure. JACC: Cardiovascular Interventions 2015;**8**:e33-34.

Acute severe occlusion of the left main coronary artery	Gul M, et al. Acute severe occlusion of the left main coronary artery following transcatheter aortic valve implantation. Anadolu Kardiyoloji Dergisi 2012;**12**:282-283. Koyama Y, et al. Left Anterior Descending Coronary Artery Obstruction Associated with an Apical Suture after Transcatheter Aortic Valve Replacement. JACC: Cardiovascular Interventions 2016;**9**:499-500.
Aortic arch rupture	Dahdouh Z, et al. Aortic arch rupture: an uncommon but fatal complication during transcatheter aortic valve implantation. Jacc: Cardiovascular Interventions 2013;**6**:416-417.
Aortic dissection	Sugrue R, et al. Trans-catheter aortic valve implantation: Adverse outcomes of 120 cases in two centres. Irish Journal of Medical Science 2012;**181**:S321. Walther T, et al. Incidence of procedural complications in 9271 consecutive tav I patients: Analysis from the German aortic valve registry." Journal of the American College of Cardiology 2014;**1**:A1942. Babin-Ebell J, et al. Life-threatening complications during transcatheter aortic valve replacement requiring surgical rescue therapy. Thoracic and Cardiovascular Surgeon. Conference: 42nd Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery Freiburg Germany. 2013;**61**:(no pagination).
Aorta perforation	Abugameh A, et al. Ascending aorta perforation following dislocation of percutaneous transcatheter aortic valve implantation (TAVI). Thoracic and Cardiovascular Surgeon. Conference: 41st Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery: One Heart One Team Freiburg Germany. Conference Start 2012;**60**:(no pagination).
Aortic rupture (abdominal)	Lange R, et al. Incidence and treatment of procedural cardiovascular complications associated with trans-arterial and trans-apical interventional aortic valve implantation in 412 consecutive patients. European Journal of Cardio-thoracic Surgery 2011;**40**:1105-1113.
Aorto-Right Ventricular Defect (lethal)	Leroux L, et al. Lethal Aorto-Right Ventricular Defect After Transcatheter Aortic Valve Implantation in a Patient With Radiation-Induced Porcelain Aorta: Notes of Caution. Canadian Journal of Cardiology 2016;**32**:135.
Apical left ventricular thrombus	Singh V, et al. Transseptal antegrade transcatheter aortic valve replacement for no-access option patients: A contemporary experience. Journal of the American College of Cardiology 2013;**1**:E1900.
Apical tear	Hassan W, et al. First middle east transcatheter aortic valve implantation (TAVI) experience: Immediate and 20 months follow-up. Catheterization and Cardiovascular Interventions 2011;**77**:S139.
Baloon rupture	Gul M, et al. Rupture of the Novaflex balloon during TAVI procedure and subsequent dissection of the right iliac arteries with ruptured balloon. Turk Kardiyoloji Dernegi Arsivi 2012;**40**:325.
Catheter induced ventricular septum defect	Babin-Ebell J, et al. Life-threatening complications during transcatheter aortic valve replacement requiring surgical rescue therapy." Thoracic and Cardiovascular Surgeon. Conference: 42nd Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery Freiburg Germany 2013;**61**:(no pagination).
Circumflex artery occlusion	Mukherjee C, et al. Rare complication of circumflex artery occlusion during transfemoral aortic valve replacement (TAVR). The international journal of cardiovascular imaging 2014;**30**:1463-1464.
Cutaneo-pericardial fistula	Scheid M, et al. Cutaneo-pericardial fistula after transapical aortic valve implantation. Interactive Cardiovascular & Thoracic Surgery 2013;**16**:558-559.

Delayed ventricular apical bleed	Soon J L, et al. The contemporary outcome of fifty two consecutive surgical transcatheter valve implantation performed in one year. EuroIntervention 2012;**8**:N212.
Distal coronary embolisation	Tsujimura A, et al. Distal coronary embolisation during transcatheter aortic valve implantation. BMJ Case Reports 2016; in press.
Early valve degeneration	Harbaoui B, et al. Early Edwards SAPIEN Valve Degeneration after Transcatheter Aortic Valve Replacement. JACC: Cardiovascular Interventions 2016;**9**:198-199.
Elliptic distortion of the aortic prosthesis	Kosek M, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve: A series of cases. Kardiologia Polska 2015;**73**:627-636.
False left ventricular apical aneurysm	Kammler J, et al. False left ventricular apical aneurysm--a rare complication after transapical aortic valve replacement. Journal of Invasive Cardiology 2011;**23**:534-535.
Guide wire thrombus formation	Wiper A, et al. Guide wire thrombus formation during trans-femoral TAVI. Cardiovascular Revascularization Medicine 2014;**15**:360-361.
Iatrogenic chordal rupture	Cincin A, et al. A Case of Iatrogenic Chordal Rupture after Transcatheter Aortic Valve Implantation Procedure Requiring a Second Valve. Journal of Heart Valve Disease 2015;**24**:133-138. D'Ancona G, et al. Iatrogenic mitral valve chordal rupture during placement of an inflatable and repositionable percutaneous aortic valve prosthesis. The Journal of heart valve disease 2015;**24**:169-172.
Iliac artery rupture	Dahdouh Z, et al. Life-threatening iliac artery rupture during transcatheter aortic valve implantation (TAVI): diagnosis and management. Heart 2013;**99**:1217-1218
Intercostal artery pseudoaneurysm	Lenders G, et al. Intercostal artery pseudoaneurysm: a rare complication of transaortic transcatheter aortic valve implantation. Interactive Cardiovascular & Thoracic Surgery 2012;**15**:550-552.
Interventricular septum rupture	Martinez MI, et al. Interventricular septum rupture after transcatheter aortic valve implantation. European Heart Journal 2012;**33**:190. Garrido JM, et al. Interventricular septal rupture after transcatheter aortic valve implantation: surgical and perioperative management. Journal of Cardiac Surgery 2014;**29**:478-481.
Late prosthesis migration and rotation	Pang PY, et al. A survivor of late prosthesis migration and rotation following percutaneous transcatheter aortic valve implantation. European Journal of Cardio-thoracic Surgery 2012;**41**:1195-1196.
Left ventricular pseudoaneurysm	Matsumoto T, et al. Transseptal closure of left ventricular pseudoaneurysm post-transapical transcatheter aortic valve replacement. JACC: Cardiovascular Interventions 2014;**7**:e177-178. Morjan M, et al. Left ventricular pseudoaneurysm following transfemoral aortic valve implantation. Journal of Cardiac Surgery 2013;**28**:510-511.
Major bleeding from the apex	Wilbring M, et al. Transapical transcatheter aortic valve implantation using a repositionable second-generation device: Initial clinical Results and further follow-up of patients treated with the JenaValveTM. Thoracic and Cardiovascular Surgeon. Conference 2014;**62**:(no pagination).
Mitral valve destruction by wire entrapment	Babin-Ebell J, et al. Life-threatening complications during transcatheter aortic valve replacement requiring surgical rescue therapy. Thoracic and Cardiovascular Surgeon. Conference: 42nd Annual Meeting of the German Society for Cardiovascular and Thoracic Surgery Freiburg Germany. 2013;**61**:(no pagination)
Multivessel coronary artery spasm	Kaneko H, et al. Multivessel Coronary Artery Spasm After Transcatheter Aortic Valve Replacement. JACC: Cardiovascular Interventions 2016;**9**:621-622.

Papillary muscle rupture	de la Torre Hernandez JM, et al. Papillary muscle rupture: first report of this complication in a retrograde transfemoral aortic valve implantation. Catheterization & Cardiovascular Interventions 2011;**78**:647-649.
Perforation of the medial circumflex branch of the common femoral artery	Shannon J, et al. Iatrogenic perforation of the medial circumflex artery following femoral venous cannulation for transcatheter aortic valve replacement, presenting with retroperitoneal hematoma and successfully managed by percutaneous embolization and coiling. Catheterization and Cardiovascular Interventions 2012;**80**:1002-1006.
Pseudoaneurysm at the left ventricular apical access site	Karimi A, et al. Percutaneous transfemoral closure of a pseudoaneurysm at the left ventricular apical access site for transcatheter aortic valve implantation. Journal of Invasive Cardiology 2015;**27**:E27-E29. Ramlawi B, et al. Minimally Invasive Repair of Left Ventricular Pseudoaneurysm after Transapical Transcatheter Aortic Valve Replacement. Texas Heart Institute Journal 2016;**43**:75-77.
Pseudoaneurysm of the apex	Dahle G, Rein KA. Surgical treatment of pseudoaneurysm of the apex after transapical transcatheter aortic valve implantation. Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery 2015;**10**:S92-S93.
Ruptured pseudoaneurysm of a renal artery	Roman AJ, et al. Dissection and ruptured pseudoaneurysm of a renal artery: a non-described complication during transcatheter aortic-valve implantation. European Heart Journal 2013;34:941.
Takotsubo syndrome	Kustrzycka-Kratochwil D, et al. CoreValve transcatheter aortic valve implantation complicated by stress cardiomyopathy (tako-tsubo) and septic shock. Postepy w Kardiologii Interwencyjnej 2012;**8**:335-337.
Valve embolisation	Higgins J, et al. Transapical aortic valve implantation: The Vancouver experience. Annals of Cardiothoracic Surgery 2012;**1**:138-144. Rezq A, et al. Effectiveness and possible complications of post dilatation in patients with residual significant aortic regurgitation following valve implantation using both edwards and corevalve systems: A single center study. Journal of the American College of Cardiology 2012;**60**:B243.

The following tables relate to articles excluded from the supporting systematic review.

Table A2: Systematic reviews on TAVI vs SAVR excluded from our analyses

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Cao, C., S. C. Ang, P. Indraratna, C. Manganas, P. Bannon, D. Black, D. Tian and T. D. Yan (2013). "Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis." Annals of Cardiothoracic Surgery 2(1): 10-23.	High-risk operable, low-risk 2 RCTs (**PARTNER 1A, STACCATO**) in 3 papers; 11 observational studies.	The available data on TAVI versus AVR for patients at a higher surgical risk showed that major adverse outcomes such as mortality and stroke appeared to be similar between the two treatment modalities.	No separate analyses for different risk levels.
Nagaraja, V., J. Raval, G. D. Eslick and A. R. Denniss (2014). "Approaches for transcatheter aortic valve replacement: A systematic review and meta-analysis." Global Heart **1)**: e82	High-risk operable, low-risk 3 RCTs (PARTNER 1A, US CoreValve, STACCATO) in 3 papers,10 propensity score matched studies, 5 case matched studies and 2 studies that provided adjusted analysis.	Randomised and observational evidence adjusted on the baseline patient's characteristics finds a similar risk for 30 days mortality, 1-year mortality, stroke, MI and acute kidney injury in TAVR and SAVR.	No separate analyses for different risk levels
Siontis, G. C., F. Praz, T. Pilgrim, D. Mavridis, S. Verma, G. Salanti, L. Sondergaard, P. Juni and S. Windecker (2016). "Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials." Eur Heart J.	High-risk operable, Intermediate-risk 4 RCTs (**PARTNER 1A**, **PARTNER 2A**, **US CoreValve**, **NOTION**) in 8 papers	Compared with SAVR, TAVI is associated with a significant survival benefit throughout 2 years of follow-up. Importantly, this superiority is observed irrespective of the TAVI device across the spectrum of intermediate and high-risk patients, and is particularly pronounced among patients undergoing transfemoral TAVI and in females.	No separate analyses for different risk levels.
Takagi, H. and T. Umemoto (2016). "Sutureless aortic valve replacement may improve early mortality compared with transcatheter aortic valve implantation: A meta-analysis of comparative studies." Journal of Cardiology 67(6): 504-512.	TAVI vs SU-AVR No RCTs; 7 observational comparative studies (enrolling a total of 945 patients) were included	Compared with TAVI, sutureless AVR may be associated with a reduction in early mortality and postoperative paravalvular aortic regurgitation.	Non-specific, seemed to have included any risk level

Table A3: Comparative studies excluded from the systematic review

Study	Risk level assessment and/or indications for TAVI	Direction of conclusions	Reason for exclusion
Amonn K, Stortecky S, Brinks H, et al. (2013). Quality of life in high-risk patients: comparison of transcatheter aortic valve implantation with surgical aortic valve replacement. Eur J Cardiothorac Surg;**43**:34-41.	High risk patients • Interdisciplinary heart team on the basis of EuroSCORE, STS score and technical feasibility of either therapy	Selected high-risk patients undergoing TAVI by using a transapical access achieve similar clinical outcomes and quality of life (QoL) compared with patients undergoing SAVR. Increased STS scores predict worse QoL outcomes.	Unclear if it is an operable, inoperable or a mixed high risk population
Appel CF, Hultkvist H, Nylander E, et al. (2012). Transcatheter versus surgical treatment for aortic stenosis: Patient selection and early outcome. Scand Cardiovasc J 2012;**46**:301-7.	Patients for whom SAVR infers an unacceptable high risk • LogEuroSCORE >15% • Patients with LogEuroSCORE <15% were not excluded	TAVI offers a safe short-term treatment with excellent good hemodynamic results in selected patients with high-risk for SAVR. Besides high logEuroSCORE, other factors influence the choice of therapy. In addition, the selection criteria for TAVI need to be refined and evaluated. The issue of paravalvular leakage and valve durability need to be addressed and may influence the patient selection.	Unclear if it is an operable, inoperable or a mixed high risk population
Bagur R, Rodés-Cabau J, Gurvitch R, , et al. (2012). Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. JACC Cardiovasc Interv;**5**:540-51.	Mean LogEuroSCORE and STS score presented in population characteristics were significantly higher in TAVI group (26±17%; 9.2±5.7%) compared with SAVR group (12±9%; 3.6±1.5%)	Transcatheter aortic valve implantation with a balloon expandable valve was complicated with the need for permanent pacemaker implantation (PPI) after the procedure in 7.3% of the patients, a rate significantly higher than the rate of 3.4% observed in SAVR patients with similar baseline ECG abnormalities.	Risk level unclear; possibly high risk
Bauer F, Coutant V, Bernard M, et al. (2013). Patients With Severe Aortic Stenosis and Reduced Ejection Fraction: Earlier Recovery of Left Ventricular Systolic Function After Transcatheter Aortic Valve Implantation Compared With Surgical Valve Replacement. Echocardiography; **30**:865-70.	High risk or contra-indicated patients for SAVR based on the inclusion criteria of the REVIVE and PARTNER European trials and the SOURCE European Registry	In patients with severe AS and reduced ejection fraction, TAVI is associated with earlier hemodynamic results and left ventricular function recovery compared with SAVR. Radial deformation may play a crucial role in this recovery, being preserved in TAVI while deteriorated during SAVR. TAVI can therefore be considered a promising alternative to AVR in this high-risk population.	Unclear if it is an operable, inoperable or a mixed risk population
Conradi L, Seiffert M, Treede H, et al. (2012). Transcatheter aortic valve implantation versus surgical aortic valve replacement: A propensity score analysis in patients at high surgical risk. J Thorac Cardiovasc Surg;**143**:64-71.	All patients were considered to be at high surgical risk owing to comorbidities with a LogEuroSCORE ≥20%.	The decision for TAVI or SAVR for treatment of aortic stenosis in high-risk patients has to be based on clinical judgment and on the individual patient's characteristics and risk factors. At present, TAVI and AVR seem to be complementary approaches for treatment of high-risk patients with severe aortic stenosis and permit a patient-orientated tailor-made treatment strategy.	Unclear if it is an operable, inoperable or a mixed high risk population
Davies JE, McAlexander WW, Sasse MF, Leesar MA, et al.(2016). Impact of Transcatheter Aortic Valve Replacement on Surgical Volumes and Outcomes in a Tertiary Academic Cardiac Surgical Practice. J Am Coll Surg;**222**:645-55.	High risk or non-operable patients. Study indications for TAVR mimicked the FDA guidelines and those of the PARTNER trial.	Transcatheter aortic valve replacement patients had more preoperative comorbidities, but no difference in postoperative morbidity or mortality and shorter length of stay. Transcatheter aortic valve replacement mortality has continued to improve.	A mixed high risk population
D'Onofrio A, Rizzoli G, Messina A, et al. (2013).Conventional surgery, sutureless valves, and transapical aortic valve replacement: What is the best option for	The main indication for TAVI was associated with 1 or more of the following: (1) porcelain aorta; (2) high surgical risk	SAVR was associated with lower 30-day mortality than TA-TAVR. SAVR was also associated with a lower risk of postoperative aortic regurgitation compared with TA-TAVR. No other significant differences	Unclear if it is an operable, inoperable or a mixed high risk population

Study	Risk level assessment and/or indications for TAVI	Direction of conclusions	Reason for exclusion
patients with aortic valve stenosis? A multicenter, propensity-matched analysis. J Thorac Cardiovasc Surg, **146**:1065-70.	(LogEuroSCORE I >20%; STS score >10%); and (3) other serious comorbidities	in outcomes among matched patients treated with SAVR, SU-AVR, and TA-TAVR were reported.	
Falcone M, Russo A, Mancone M, et al. (2014). Early, intermediate and late infectious complications after transcatheter or surgical aortic-valve replacement: a prospective cohort study. Clin Microbiol Infect;**20**:758–63.	Patients were qualified for a TAVI if they fulfilled the following criteria: (i) age ≥75 years and a LogEuroSCORE ≥20% or (ii) LogEuroSCORE <20% and at least one of the following: cirrhosis of liver, pulmonary insufficiency (FEV1 ≤ 1 L) or porcelain aorta	Despite the high frequency of coexisting illnesses in patients undergoing TAVI, the frequency of infectious complication was very low. TAVI as a reasonable and safe option in inoperable or high-risk patients with severe symptomatic aortic stenosis.	Risk level unclear; possibly high risk or inoperable
Forsberg LM, Tamás E, Vánky F, et al (2011). Left and right ventricular function in aortic stenosis patients 8 weeks post-transcatheter aortic valve implantation or surgical aortic valve replacement. Eur J Echocardiogr;**12**:603-11.	High risk or contra-indicated patients for SAVR ass assessed by a team of surgeons and cardiologists	Patients with severe AS and a high surgical risk profile have a favourable change in longitudinal left ventricular and right ventricular function 8 weeks after TAVI.	Unclear if it is an operable, inoperable or a mixed risk population
Giannini C, Petronio AS, Nardi C et al (2011). Left ventricular reverse remodelling in percutaneous and surgical aortic bioprostheses: an echocardiographic study. J Am Soc Echocardiogr 2011;**24**:28-36.	High risk or inoperable	Haemodynamic performance after TAVI was shown to be superior to that after SAVR in terms of trans prosthetic gradient, left ventricular (LV) ejection fraction, and the prevention of severe patient prosthesis mismatch(PPM), but with a higher incidence of aortic regurgitation. Furthermore, LV reverse modelling was observed in all patients in the absence of PPM, while the same remodelling occurred in TAVI subgroup when sever PPM was present.	A mixed high risk population
Hannan EL, Samadashvili Z, Stamato NJ, , et al. (2016). Utilization and 1-Year Mortality for Transcatheter Aortic Valve Replacement and Surgical Aortic Valve Replacement in New York Patients With Aortic Stenosis. JACC Cardiovasc Interv **9**:578-85.	Low-medium (<3%) and high risk (≥3%) patients based on NYS in-hospital/30-day mortality risk model for isolated valve surgery	TAVR has assumed a much larger share of all aortic valve replacements for severe aortic stenosis, and the average level of pre-procedural risk has decreased substantially. There are no differences between 1-year mortality rates for TAVR and SAVR patients.	A mixed population. Unclear whether high risk patients are operable or not
Hoffmann R, Almutairi B, Herpertz R, et al. (2013).Two-year mortality after transcatheter aortic valve implantation versus medical therapy for high-surgical risk or inoperable aortic stenosis patients. J Heart Valve Dis; **22**:71-8.	High operative risk (LogEuroSCORE>20%) or other conditions related to a high operative risk such as significant frailty	In high surgical risk or inoperable symptomatic aortic stenosis patients, the one and two year follow up mortalities of patients treated with TAVI was significantly lower than after medical therapy. Predicators of mortality, in addition to treatment strategy, were pulmonary hypertension and EuroSCORE.	Unclear if it is an operable, inoperable or a mixed high risk population
Holzhey DM, Shi W, Rastan A, Borger MA, et al (2012). Transapical versus conventional aortic valve replacement--a propensity-matched comparison. Heart Surg Forum;**15**:E4-8.	All patients >75 years and with a EuroSCORE >9%	Even with all the latest successes in catheter-based AV implantation, the conventional surgical approach is still a very good treatment option with excellent long-term results, even for older, high-risk patients.	Risk level unclear
Idrees J, Roselli EE, Raza S, et al.(2015) Aborted sternotomy due to unexpected porcelain aorta: does transcatheter aortic valve replacement offer an alternative choice? J Thorac Cardiovasc Surg **149**:131-4.	The choice of procedure type was based on a thorough preoperative assessment to determine the operative risk, anatomic feasibility, and need for additional procedures for cardiac comorbidities	Both surgical aortic valve replacement and transcatheter aortic valve replacement are safe and effective options after aborted sternotomy in patients with porcelain aorta who are referred to a high-risk valve centre. Procedure selection may be tailored to individual patients on the basis of aortic morphology and comorbidities. Patients with aortic	Risk level unclear

Study	Risk level assessment and/or indications for TAVI	Direction of conclusions	Reason for exclusion
		stenosis at risk for calcific aortic disease should be screened with cross-sectional imaging preoperatively.	
Im E, Hong MK, Ko YG, Shin DH, et al. (2013). Comparison of Early Clinical Outcomes Following Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement versus Optimal Medical Therapy in Patients Older than 80 Years with Symptomatic Severe Aortic Stenosis. Yonsei Med J;**54**:596–602.	High risk or inoperable	Treatment with TAVI was associated with lower event rates compared to SAVR or optimal medical therapy. Therefore, TAVI may be considered as the first therapeutic strategy in selected patients aged ≥80 years with symptomatic severe AS.	A mixed high risk population
Johansson M, Nozohoor S, Kimblad PO, (2011). Transapical Versus Transfemoral Aortic Valve Implantation: A Comparison of Survival and Safety. Ann Thorac Surg;**91**:57-63.	All patients were at high surgical risk or presented technical challenges to conventional AVR (risk estimated using the LogEuroSCORE and STS score, together with clinical judgment)	The vascular complications occurring when using the transfemoral (TF) approach were probably related to a combination of a wide introducer sheath and heavily calcified femoral arteries in a high-risk population. No serious complications were encountered when using the Transapical (TA) approach. After propensity-score matching, survival with both the TA and TF approaches is similar to that after SAVR.	Unclear if it is an operable, inoperable or a mixed high risk population
Kala P, Tretina M, Poloczek M, et al. (2013). Quality of life after transcatheter aortic valve implantation and surgical replacement in high-risk elderly patients. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub;**157**:75-80.	High risk patients >75 years with a LogEuroSCORE > 15%	At one year, the general quality of life of high-risk patients had significantly improved after transcatheter aortic valve implantation with a positive trend in surgically treated patients.	Unclear if it is an operable, inoperable or a mixed risk population
Keyl C, Schneider J, Beyersdorf F, et al. (2016). Right ventricular function after aortic valve replacement: a pilot study comparing surgical and transcatheter procedures using 3D echocardiography. Eur J Cardiothorac Surg **49**:966-71.	Mean LogEuroSCORE presented in population characteristics were significantly higher in TAVI group (11.9±5.8%) compared with SAVR group (7.0±3.3%)	Right ventricular (RV) longitudinal contraction decreased after SAVR, whereas RV transverse contraction increased. Both parameters did not change after TAVI. RV ejection fraction and RV stroke volume remained constant irrespective of the technique of aortic valve replacement, thus indicating that global systolic RV function is not compromised after SAVR.	Risk level unclear
Kobrin DM, McCarthy FH, Herrmann HC, et al. (2015).Transcatheter and Surgical Aortic Valve Replacement in Dialysis Patients: A Propensity-Matched Comparison. Ann Thorac Surg 2015;**100**:1230-6.	High risk or inoperable dialysis patients	TAVR in dialysis patients is associated with decreased survival compared with non-dialysis patients; however, it is comparable with SAVR in high risk dialysis patients based on a propensity-matched comparison	A mixed high risk population
Kocaaslan C, Ketenci B, Yılmaz M, et al. (2016). Comparison of Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement to Improve Quality of Life in Patients >70 Years of Age with Severe Aortic Stenosis. Braz J Cardiovasc Surg, **31**:1-6.	A hospital council decided on the type of procedure to be performed. Mean LogEuroSCORE presented in population characteristics for the TAVI group was 9.75±1.27%	The significantly higher positive increase in quality of life in the transcatheter aortic valve implantation group at 3 months postoperatively compared to the surgical aortic valve replacement group.	Risk level unclear
Latib A, Maisano F, Bertoldi L, et al. (2012). Transcatheter vs surgical aortic valve replacement in intermediate-surgical-risk patients with aortic stenosis: A propensity	Included moderate-to-high risk patients. High-risk was defined as Logistic Euro-SCORE ≥20%, or STS≥10%, or conditions not captured by the 2 scores that the cardiac surgeon considered to increase	TF-TAVR and SAVR were associated with similar mortality rates during follow-up but with a different spectrum of peri-procedural complications. Furthermore, the survival rate after TF-TAVR in this group of elderly patients with intermediate Society of Thoracic Surgeons score was encouraging.	A mixed moderate (or low)- to high-risk population

Study	Risk level assessment and/or indications for TAVI	Direction of conclusions	Reason for exclusion
score–matched case-control study. Am Heart J;**164**:910-7.	the risk for standard SAVR. TAVR vs SAVR risk scores (mean±SD): Logistic Euro-SCORE scores 23.2±15.1 vs 24.4±13.4 and STS score 4.6±2.3 vs 4.6±2.6.		
McCabe JM, Huang PH, Riedl LA, et al. (2014). Incidence and Implications of Idiopathic Thrombocytopenia Following Transcatheter Aortic Valve Replacement With the Edwards Sapien Valves: A Single Center Experience. Catheter Cardiovasc Interv, **83**:633-41.	High surgical risk	Thrombocytopenia following TAVR is a frequent but generally self-limited process. The etiology of this phenomenon is unknown.	Unclear if it is an operable, inoperable or a mixed high risk population
Möllmann H, Bestehorn K, Bestehorn M, et al. (2016) In-hospital outcome of transcatheter vs. surgical aortic valve replacement in patients with aortic valve stenosis: complete dataset of patients treated in 2013 in Germany. Clin Res Cardiol;**105**:553-9.	Patients were categorized into four risk groups using the LogEuroSCORE I: <10, 10–20, 20–30, and >30%	This study demonstrates that TAVI provides excellent outcomes in all risk categories. Compared with SAVR, TV-TAVI yields similar in-hospital mortality among low-risk patients and lower in-hospital mortality among intermediate and high-risk patient populations.	A mixed population of all risk levels
Motloch LJ, Reda S, Rottlaender D, et al. (2012).Postprocedural Atrial Fibrillation After Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement. Ann Thorac Surg; **93**:124-31.	Patients who were denied SAVR due to high perioperative risk.	TAVI, compared with SAVR, reduces the risk of periprocedural atrial fibrillation.	A mixed high risk population
Nemec P, Ondrasek J, Malik P, et al. (2012). Comparison of the surgical and transcatheter aortic valve replacement in high-risk patients. Cor et Vasa; **54**:e76-83.	High risk patients >75 years with a LogEuroSCORE > 15%	TAVI is a safe method for treatment of aortic stenosis in high-risk patients and its early results are comparable with surgical aortic valve replacement. The TF and TA approaches are equally efficient, with similar outcomes and complication rates. criteria for TAVI approaches will expand.	Unclear if it is an operable, inoperable or a mixed risk population
Olsson K, Nilsson J, Hörnsten Å, Näslund U. (2016) Patients' self-reported function, symptoms and health-related quality of life before and 6 months after transcatheter aortic valve implantation and surgical aortic valve replacement. Eur J Cardiovasc Nurs; Epub ahead of print.	Patients were not accepted for surgery due to high risk	Found no change in cognitive function or dependence at follow-up. There was no difference in the size of improvement between groups.	A mixed high risk population; possibly inoperable
Onorati F, D'Errigo P, Grossi C, et al. (2014) Effect of severe left ventricular systolic dysfunction on hospital outcome after transcatheter aortic valve implantation or surgical aortic valve replacement: Results from a propensity-matched population of the Italian OBSERVANT multicenter study. J Thorac Cardiovasc Surg ;**147**:568-75.	High risk	In patients with severe left ventricular systolic dysfunction, both TAVI and AVR are valid treatment options, with comparable hospital mortality and periprocedural morbidity.	Unclear if it is an operable, inoperable or a mixed high risk population

Study	Risk level assessment and/or indications for TAVI	Direction of conclusions	Reason for exclusion
Pilgrim T, Wenaweser P, Meuli F, et al. (2011). Clinical Outcome of High-Risk Patients with Severe Aortic Stenosis and Reduced Left Ventricular Ejection Fraction Undergoing Medical Treatment or TAVI. PLoS One;**6**:e27556.	High risk or inoperable	TAVI in patients with severely reduced left ventricular function may be performed safely and is associated with rapid recovery of systolic left ventricular function and heart failure symptoms.	A mixed high risk population
Retzlaff B, Wessel N, Riedl M, Gapelyuk A, Malberg H, Bauernschmitt N, et al. Preserved autonomic regulation in patients undergoing transcatheter aortic valve implantation (TAVI) – a prospective, comparative study. Biomed Tech (Berl) 2011;**56**:185-93.	High risk; no further details	In contrast to patients undergoing conventional open surgery, there are fewer alterations of the cardiovascular autonomic system in patients with TAVI.	Unclear if it is an operable, inoperable or a mixed high risk population
Stöhr R, Dohmen G, Herpertz R, et al. (2011) Thirty-day outcome after transcatheter aortic valve implantation compared with surgical valve replacement in patients with high-risk aortic stenosis: a matched comparison. Coron Artery Dis; **22**:595-600.	High operative risk (LogEuroSCORE>20%) or other conditions related to a high operative risk such as significant frailty	In high-surgical risk patients, TAVI can be performed at a mortality risk comparable with conventional surgery with a reduced length of post interventional intensive care unit stay and less need for dialysis.	Unclear if it is an operable, inoperable or a mixed high risk population
Stortecky S, Brinks H, Wenaweser P, et al. (2011).Transcatheter Aortic Valve Implantation or Surgical Aortic Valve Replacement as Redo Procedure After Prior Coronary Artery Bypass Grafting. Ann Thorac Surg;**92**:1324-30.	LogEuroSCORE was significantly higher for the TAVI cohort (35.5±17), whereas the STS score revealed no differences between the two groups (TAVI vs SAVR)	In elderly, high-risk patients after prior CABG, conventional aortic valve replacement and TAVI are comparable treatment options with favorable clinical outcome.	Risk level unclear
Sulženko J, Toušek P, Kočka V, Bednář F, Línková H, Petr R, et al. Degenerative changes and immune response after transcatheter aortic valve implantation. Comparison with surgical aortic valve replacement. J Cardiol 2016; Epub ahead of print.	TAVI patients had more comorbidities evaluated in LogEuroSCORE I [TAVI: 21.0 (5.0;46.0) vs. SAVR: 6.15 (2.54; 11.17)]	Minimal degenerative changes on TAVI prosthesis were observed in mid- and long-term follow-up. Systemic immune response did not differ between patients after TAVI and SAVR.	Risk level unclear
Tamburino C, Barbanti M, Capodanno D, , et al. (2012). Comparison of Complications and Outcomes to One Year of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis. Am J Cardiol;**109**:1487-93.	High risk or contra-indicated patients for SAVR	TAVI was not associated with a higher risk of 1-year MACCEs compared to SAVR.	Unclear if it is an operable, inoperable or a mixed high risk population
Thongprayoon C, Cheungpasitporn W, Srivali N, et al. (2016). AKI after Transcatheter or Surgical Aortic Valve Replacement. J Am Soc Nephrol 2016;**27**:1854-60.	High risk patients	No significant differences existed between the TAVR and SAVR groups in postoperative AKI, major adverse kidney events or mortality >6 months after surgery. Thus, TAVR did not affect postoperative AKI risk. Because it is less invasive than SAVR, TAVR may be preferred in high-risk individuals.	Unclear if it is an operable, inoperable or a mixed high risk population

Study	Risk level assessment and/or indications for TAVI	Direction of conclusions	Reason for exclusion
Tokarek T, Siudak Z, Dziewierz A, et al. (2016). Assessment of Quality of Life in Patients After Surgical and Transcatheter Aortic Valve Replacement. Catheter Cardiovasc Interv;**88**:E80-8.	High risk patients although reported mean LogEuroSCORE 9.5 (7-14)%	TAVI improves health related quality of life in perioperative and 12 months observation in comparison with mini-thoracotomy, mini-sternotomy and SAVR.	Unclear if it is an operable, inoperable or a mixed risk population
Uddin A, Fairbairn TA, Djoukhader IK et al. (2015). Consequence of cerebral embolism after transcatheter aortic valve implantation compared with contemporary surgical aortic valve replacement: effect on health-related quality of life. Circ Cardiovasc Interv;**8**:e001913.	TAVI patients were selected by a multidisciplinary heart team in accordance with contemporary UK guidance	Cerebral microinfarctions are more common after TAVI compared with SAVR but seem to have no negative effect on early (30 days) or medium term (6 months) health-related quality of life. Aortic atheroma (TAVI) and concomitant coronary artery bypass grafting (SAVR) are independent risk factors for cerebral microinfarction	Risk level unclear
Wenaweser P, Pilgrim T, Kadner A, et al. (2011) Clinical Outcomes of Patients With Severe Aortic Stenosis at Increased Surgical Risk According to Treatment Modality. J Am Coll Cardiol;**58**:2151-62.	At increased surgical risk (EuroSCORE >15% and/or with comorbid conditions)	Clinical outcomes of TAVI and SAVR seem similar among carefully selected patients with severe symptomatic AS at increased risk.	Risk level unclear; possibly high risk
Wendt D, Al-Rashid F, Kahlert Pet al. (2015). Conventional aortic valve replacement or transcatheter aortic valve implantation in patients with previous cardiac surgery. J Cardiol;**66**:292-7.	High-risk patients with a LogEuroSCORE-I > 20%, or at high risk due to the presence of other coexisting illnesses not reflected by the EuroSCORE	Patients with cardiac reoperation, TAVI comes with similar outcomes when compared to surgical AVR. On the other hand, conventional redo-AVR is still a valuable and safe treatment option	Unclear if it is an operable, inoperable or a mixed high risk population

Table A4 (a): Excluded non-comparative observational studies reporting long-term* safety outcomes and reason for exclusion

Study	N	TAVI		Population risk level	Follow-up period	Key long-term outcomes	Reason for exclusion
		Valve	Route				
Barbanti et al. 2016	995	Medtronic CoreValve	Mainly transfemoral (subclavian or direct aortic in some cases)	2 groups: STS≤7% (n=697) vs. STS>7% (n=298)	3 years	All-cause and cardiovascular mortality, neurologic events (stroke and TIA), MI, bleeding, vascular complications and AKI	Varying levels of surgical risk.Data not informative
Collas et al. 2015	861	Edwards SAPIEN or Medtronic CoreValve	Mainly transfemoral but also transapical, subclavian or direct aortic	Not candidates for SAVR (low, intermediate and high risk EuroSCORE cohorts)	3 years	Overall survival	Varying levels of surgical risk. Data not informative
D'Onofrio et al. 2016	338	Medtronic CoreValve or Edwards SAPIEN, Edwards SAPIEN XT, Edwards SAPIEN 3	Transfemoral for CoreValve; transfemoral or transapical for SAPIEN	Unsuitable or at high risk for SAVR	5 years	Overall survival	Mixed high risk population; follow-up period covered by comparative studies
Holzhey et al. 2012	439	Cribier Edwards, Edwards SAPIEN THV, Edwards SAPIEN XT	Transapical	Mixed risk level; possibly high risk	~5.6 years	Overall survival and hemodynamic performance	Varying levels of surgical risk. Data not informative
Unbehaun 2015	730	Edwards SAPIEN THV, Edwards SAPIEN XT	Transapical	Unsuitable or at high risk for SAVR	Up to 5 years (median 1.56years)	Overall survival	Mixed high risk population; follow-up period covered by comparative studies
Wang 2014	599	No details	No details	Consecutive patients. Mixed risk level	Up to 5 years (mean ~2.5 years)	Overall survival	Varying levels of surgical risk. Data not informative

*Long-term in this case refers to studies with follow-up: i) > 5 years for patients unsuitable for SAVR and patients for whom SAVR was considered suitable but poses a high risk; ii) > 2 years for patients with intermediate or low risk; iii) > 1 year for studies reporting valve function/durability.

Table A4(b). Included non-comparative observational studies reporting long-term safety outcomes

Study	Population risk level	TAVI valve	Follow-up period	Key long-term outcomes	Key finding
Barbanti et al. 2015	353 high risk patients; unclear whether suitable for SAVR or not (transfemoral: 89.8%, subclavian: 10.2%). Age: mean 81.5 (SD6.3) years. Risk score: median LogEuroSCORE 21.5% (15-31); Mean STS 9.5% (SD10)	Medtronic CoreValve 100%	Only consecutive patients with 5-year follow-up were included in analysis	• Prosthetic valve failure • Neurological event rate	• Late prosthesis failure occurred in 5 cases(1.4%); late mild stenosis observed in 10 cases (2.8%). No other cases of structural or non-structural deterioration were observed. Transaortic gradient slightly increased at 5 years 12.8 (SD10.9) mm Hg • Overall neurological event rate was 7.5% of which more thatn two-thirds occurred early after the procedure
Bouleti et al. 2015	123 patients considered to be unsuitable or at high risk for surgery (transfemoral: 68.3%, transapical: 30.1%). Age: mean 81.5 (SD8.4) years. Risk score: EuroSCORE II 7.8% (SD5.6); STS 7.1% (SD4.7)	• Edwards SAPIEN 90.3% • Medtronic CoreValve 9.7%	Up to 6 years (median 3.6 years IQR: 2.6-4.7)	• Survival rate • Major stroke • Prosthetic valve disfunction	Time-to-event data: • All-cause survival at 6 years was 31% ± 5%; Cardiovascular survival rate at 6 years was 66% ± 5% • Cumulative rates of major stroke at 6 years after TAVI were 16.0% ± 4.0%. There was no difference in the rates of stroke according to the presence or absence of atrial fibrillation (16.2% ± 7.0% and 17.0% ± 5.0% respectively, p=0.42). • 5 patients had prosthetic disfunction: 3/5 had stenosis at 1.3, 3.2 and 5 years; 1/5 had aortic regurgitation grade 3 at 4.8 years and 1/5 had aortic regurgitation grade 4 at 2.o years
Ludman et al. 2015 UK TAVI Registry	3980 patients high risk patients; unclear whether suitable for SAVR or not (transfemoral: 71.2%, transapical: 19.2%, subclavian: 4.8%, direct aortic 4.8%). Age: mean 81.3 (SD7.6) years. Risk score: LogEuroSCORE 21.9% (SD13.7)	• Edwards SAPIEN (n=2036, 51.8%) • Medtronic CoreValve (n=1897, 48.2%) • Other valve (n=41, 1%)	6-8 years	Overall survival (n=3671)	Mortality / Survival / Upper 95%CI / Lower 95%CI 6 years: 0.6271 / 0.3729 / 0.3306 / 0.4153 7 years: 0.707 / 0.2930 / 0.2096 / 0.3813 8 years: no data / 0.2930 / 0.2096 / 0.3813
Papadopoulos et al. 2016	312 patients considered to be unsuitable or at high risk for surgery (transapical: 100%). Age: mean 79.8 (SD5.8) years.	• Cribier Edwards • Edwards Sapien • Edwards Sapien XT • Edwards Sapien 3	At the time of discharge, at 6 months, at 12 months and yearly thereafter.	Prosthetic valve function	• Late follow-up at 4.1 (SD2.3) years, n=174 patients: Improvement of effective aortic orifice area: 1.52 (SD0.2) cm^2 Paravalvular leaks (grade I to II): 59 (34%) Paravalvular leaks (>grade II): 19 (11%) Mean ejection fraction: 0.53 (SD0.09)

Study	Population risk level	TAVI valve	Follow-up period	Key long-term outcomes	Key finding
	Risk score: LogEuroSCORE II 23.9% (SD17.2); STS 9.8% (SD8.6)		11 patients with mean follow-up time beyond 8 years		Decrease in mean transvalvular aortic gradient • Overall survival data at 8-10 years from graph ~40% Improvement of effective aortic orifice area 1. (SD0.5) cm^2 and mean transvalvular aortic gradient Paravalvular leaks (grade I to II): 4/11 (36%) Paravalvular leaks (>grade II): 1/11 (9%) Mean ejection fraction: 0.49 (SD0.11) Stent reconstruction showed stable structural behaviour of the stent beyond 8 years.
Rodés-Cabau et al. 2012	339 patients unsuitable or at very high risk for surgery (transfemoral: 48%, transapical: 52%). Age: mean 81 (SD 8) years Risk score: STS 9.8% (SD 6.4)	• Cribier-Edwards valve (n=57) • Edwards SAPIEN valve (n=275) • Edwards SAPIEN XT valve (n=7)	Most patients were followed at 1 year after the procedure and annually thereafter	Prosthetic valve durability	A mild non-clinically significant decrease in valve area occurred at 2-year follow-up ($p<0.01$), but no further reduction in valve area was observed up to 4-year follow-up. No changes in residual aortic regurgitation and no cases of structural valve failure were observed during the follow-up period.
Salinas et al. 2016	79 patients considered to be unsuitable or at high risk for surgery (transfemoral: 81%, transapical: 19%). Age: mean 82.3 (SD6.1) years. Risk score: LogEuroSCORE 16.9% (SD9.1); STS 5.9% (SD2.9)	• Edwards Sapien (n=14, 17.7%) • Edwards Sapien XT (n=65, 82.3%)	2.5 to max 6.5 years	Prosthetic valve dysfunction	Follow-up >2.5 years: a 15.3% prosthetic valve dysfunction rate according to VARC-2 (moderate aortic regurgitation and/or mean gradient of 20 mmHg to 25 mmHg) without need for repeat valve replacement. There were no documented cases of aortic complication, mitral valve lesions, endocarditis, or prosthetic valve thrombosis.
Tan et et al. 2015	47 patients at risk of annular injury who underwent TAVI Age: 82 (SD 7.6) years. Risk score: STS 7.8% (SD 3.5)	Excessive oversizing of a balloon expandable Edwards SAPIEN XT valve	1 year	Prosthetic valve function and frame durability	There was no evidence of stent frame recoil, deformation, or fracture at 1 year.

Appendix B: Related NICE guidance for transcatheter aortic valve implantation

Guidance	Recommendations
Interventional procedures	**Transcatheter aortic valve implantation for aortic stenosis. NICE guideline IPG421 (2012; current guidance)** ***1 Guidance*** This document replaces previous guidance on transcatheter aortic valve implantation for aortic stenosis (interventional procedure guidance 266). 1.1 Evidence on the safety of transcatheter aortic valve implantation (TAVI) for aortic stenosis shows the potential for serious but well-recognised complications. 1.2 For patients with aortic stenosis who are considered to be unsuitable for surgical aortic valve replacement (SAVR; see sections 1.6 and 2.1.3) the evidence on the efficacy of TAVI is adequate. For these patients, TAVI may be used with normal arrangements for clinical governance, consent and audit. Details of all patients should be entered into the UK Central Cardiac Audit Database. 1.3 For patients with aortic stenosis for whom SAVR is considered suitable but to pose a high risk (see sections 1.5, 1.6 and 2.1.3) the evidence on the efficacy of TAVI is inadequate. For these patients TAVI should only be used with special arrangements for clinical governance, consent and data collection or research. NICE encourages clinicians to enter suitable patients into the UK TAVI trial. In addition, details of all patients should be entered into the UK Central Cardiac Audit Database. 1.4 For patients with aortic stenosis for whom SAVR is considered suitable and not to pose a high risk (see sections 1.6 and 2.1.3) the evidence on the efficacy of TAVI is inadequate. For these patients TAVI should only be used in the context of research. NICE encourages clinicians to enter suitable patients into the UK TAVI trial. In addition, details of all patients should be entered into the UK Central Cardiac Audit Database. 1.5 Clinicians wishing to undertake TAVI for patients with aortic stenosis for whom SAVR is considered suitable but to pose a high risk (see section 1.3) should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the risk of stroke and death, and the uncertainty about the procedure's efficacy in the long term. Provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended.

	1.6 Patient selection should be carried out by a multidisciplinary team including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist and an expert in cardiac imaging. The multidisciplinary team should determine the risk level for each patient. 1.7 TAVI is a technically challenging procedure that should be performed only by clinicians and teams with special training and experience in complex endovascular cardiac interventions. Units undertaking this procedure should have both cardiac and vascular surgical support for emergency treatment of complications. 1.8 NICE encourages further research into TAVI for aortic stenosis. In particular, NICE encourages clinicians to enter all suitable patients into the UK TAVI trial. Information from research trials that will be useful for future guidance includes patient selection criteria and comparisons between TAVI and SAVR in patients who would be suitable for either procedure. Outcomes should include incidence of stroke and other adverse events, symptom relief, quality of life, occurrence of aortic regurgitation, and valve durability in the short and long term. 1.9 NICE may review this procedure on publication of further evidence.
	Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction. NICE guideline IPG 504 (2014). ***1 Recommendations*** 1.1 For patients with aortic bioprosthetic valve dysfunction for whom surgical aortic valve replacement (SAVR) is considered to be unsuitable (see section 1.6), the evidence on the safety and efficacy of valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) is adequate. For these patients, ViV-TAVI may be used with normal arrangements for clinical governance, consent and audit. Details of all patients should be entered into the UK Central Cardiac Audit Database. 1.2 For patients with aortic bioprosthetic valve dysfunction for whom surgical aortic valve replacement (SAVR) is considered to be suitable but to pose a high risk (see sections 1.4, 1.5 and 1.6), the evidence on the safety and efficacy of valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) is inadequate. For these patients, ViV-TAVI should only be used with special arrangements for clinical governance, consent and data collection or research. Details of all patients should be entered into the UK Central Cardiac Audit Database. 1.3 For patients with aortic bioprosthetic valve dysfunction for whom surgical aortic valve replacement (SAVR) is considered to be suitable and not to pose a high risk (see sections 1.5 and 1.6), the evidence on the safety and efficacy of valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) is inadequate. For these patients, ViV-TAVI should only be used in the

	context of research. In addition, details of all patients should be entered into the UK Central Cardiac Audit Database. 1.4 Clinicians wishing to carry out valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) for patients with aortic bioprosthetic dysfunction for whom surgical aortic valve replacement (SAVR) is considered to be suitable but to pose a high risk (see section 1.2) should take the following actions: Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the risk of death, and the uncertainty about the procedure's efficacy in the long term. • Provide them with clear written information. In addition, the use of NICE's information for the public is recommended. Patient selection should be carried out by a multidisciplinary team including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist and an expert in cardiac imaging. The multidisciplinary team should determine the risk level for each patient. 1.5 Valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) is a technically challenging procedure that should only be done by clinicians and teams with special training and experience in complex endovascular cardiac interventions, including regular experience in the use of TAVI. Units doing this procedure should have both cardiac and vascular surgical support for emergency treatment of complications. 1.6 NICE encourages further research into valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) for aortic bioprosthetic dysfunction. Comparative studies between ViV-TAVI and surgical aortic valve replacement (SAVR) for patients who are judged to have a low risk from SAVR should describe patient selection clearly and should report fully on complications and valve durability in the short and long term. 1.7 NICE may review this procedure on publication of further evidence.
	Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. NICE guideline IPG541. (2015). ***1 Recommendations*** These recommendations apply only to patients for whom open surgical valve implantation is unsuitable. 1.1 The current evidence on the safety of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis shows the potential for

	serious complications. However, this is in patients for whom open surgical valve implantation is unsuitable, who have severe symptoms and a high risk of death. The evidence on efficacy shows generally good symptom relief in the short term, but is based on very small numbers of patients. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.1.2 Clinicians wishing to do transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis should: • Inform the clinical governance leads in their NHS trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy in the long term, and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. • Enter details about all patients having transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis onto the National Institute for Cardiovascular Outcomes Research database (NICOR) and review local clinical outcomes. 1.3 Patient selection should be done by a multidisciplinary team including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist and an expert in cardiac imaging. The multidisciplinary team should determine the risk level for each patient and review their suitability for alternative medical or surgical treatments. 1.4 Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis should only be done by clinicians and teams with special training and experience in complex endovascular cardiac interventions, including regular experience in transcatheter valve implantation procedures. Units doing these procedures should have both cardiac and vascular surgical support for emergency treatment of complications. 1.5 NICE encourages further research into transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. This may include prospective observational studies. Studies should include details on patient selection, functional outcomes, quality of life, survival and complications. Studies should report long-term follow-up of clinical outcomes and valve durability. NICE may update this guidance on publication of further evidence.
	Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. NICE guideline IPG 436 (2013). 1 Guidance

	This document replaces previous guidance on percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction (interventional procedure guidance 237). 1.1 The evidence on percutaneous pulmonary valve implantation (PPVI) for right ventricular outflow tract (RVOT) dysfunction shows good short-term efficacy. There is little evidence on long-term efficacy but it is well documented that these valves may need to be replaced in the longer term. With regard to safety there are well-recognised complications, particularly stent fractures in the longer term, which may or may not have clinical effects. Patients having this procedure are often very unwell and might otherwise need open heart surgery (typically reoperative) with its associated risks. Therefore, this procedure may be used with normal arrangements for clinical governance, consent and audit. 1.2 The procedure should be performed only in specialist units and with arrangements in place for cardiac surgical support in the event of complications. 1.3 Patient selection should be carried out by a multidisciplinary team including a cardiologist with a special interest in congenital heart disease, an interventional cardiologist and a cardiothoracic surgeon with a special interest in congenital heart disease. 1.4 This is a technically challenging procedure that should be performed only by clinicians with training and experience in interventional cardiology and congenital heart disease. 1.5 Clinicians should enter details about all patients undergoing PPVI for RVOT dysfunction onto the UK Central Cardiac Audit Database (UK CCAD). They should audit and review clinical outcomes locally, and in particular collect information on long-term outcomes.
	Sutureless aortic valve replacement for aortic stenosis. NICE guideline IPG456 (2013). **1 Recommendations** There is evidence of limited quality supporting the efficacy of sutureless aortic valve replacement for aortic stenosis in the short term. The evidence on safety raises no major concerns in the short term apart from the risk of paravalvular leak. There is concern about the risks of paravalvular and central leaks in the longer term. Most of the evidence on sutureless aortic valve replacement for aortic stenosis is from patients who would be at high risk from standard surgical aortic valve replacement and there is negligible comparative evidence versus standard surgery. 1.1 For patients with aortic stenosis for whom surgical aortic valve replacement is considered suitable but for whom it would pose a high risk, sutureless aortic valve replacement for aortic stenosis should only be used with special arrangements for clinical governance, consent and data collection or research. Clinicians wishing to undertake sutureless aortic valve replacement for these patients should take the following actions:

	•Inform the clinical governance leads in their trusts. •Ensure that patients understand the uncertainty about the procedure's safety and efficacy, and other treatment options, and provide them with clear written information. In addition, the use of NICE's information for the public is recommended. 1.2 For patients with aortic stenosis for whom surgical aortic valve replacement is considered suitable and for whom it would not pose a high risk, sutureless aortic valve replacement for aortic stenosis should only be used in the context of research. 1.3 Patient selection should be done by a multidisciplinary team which includes cardiologists and cardiac surgeons. 1.4 Specific training is important for this procedure and surgeons should perform their initial procedures with an experienced mentor. 1.5 Clinicians should enter details about all patients undergoing sutureless aortic valve replacement for aortic stenosis onto the UK Central Cardiac Audit Database. 1.6 NICE encourages further research into sutureless aortic valve replacement for aortic stenosis. Studies should document patient selection, aortic cross-clamp times, cardiopulmonary bypass times, perioperative morbidity and specifically the incidence of paravalvular (and central) leaks in the short and long term. Research comparing outcomes of the procedure against those of standard surgical aortic valve replacement would be useful.
	Percutaneous fetal balloon valvuloplasty for aortic stenosis. NICE guideline IPG 175 (2006). **1 Guidance** 1.1 Current evidence on the safety and efficacy of percutaneous fetal balloon valvuloplasty for aortic stenosis does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake percutaneous fetal balloon valvuloplasty for aortic stenosis should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that parents understand the uncertainty about the procedure's safety and efficacy. Clinicians should provide parents with clear written information, and with counselling and support both before and after the procedure. In addition, use of the Institute's information for the public is recommended. • Audit and review the clinical outcomes of percutaneous fetal balloon valvuloplasty for aortic stenosis.

	1.3 This procedure should only be performed in centres specialising in invasive fetal medicine and in the context of a multidisciplinary team including a consultant in fetal medicine, a paediatric cardiologist, a neonatologist, a specialist midwife and a paediatric cardiac surgeon. 1.4 An intention-to-treat registry has been developed by the Association for European Paediatric Cardiology, and clinicians are encouraged to enter all cases into this registry. 1.5 Further publication on the criteria for patient selection will be useful. The Institute may review the procedure upon publication of further evidence.
	Balloon valvuloplasty for aortic valve stenosis in adults and children. NICE guideline IPG 78 (2004). ***1 Guidance*** 1.1 Current evidence on the safety and efficacy of balloon valvuloplasty for aortic valve stenosis in adults and children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 In adults, the procedure should only be used to treat patients who are unsuitable for surgery, as the efficacy is usually shortlived. 1.3 In infants and children, the procedure should be undertaken in specialist paediatric cardiology units. 1.4 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients into this database.

Appendix C: Literature search for transcatheter aortic valve implantation

Electronic databases including: The Cochrane Library (Wiley) (CDSR, DARE, HTA and CENTRAL), CRD Centre for Reviews and Dissemination Databases (DARE, NHS EED and HTA), MEDLINE (Ovid), MEDLINE in Process (Ovid), EMBASE (Ovid), ZETOC (British Library) and PubMed (US NLH) were searched from March 2011 (April 19th 2011 being the date on which the electronic searches for the NICE rapid overview were conducted) to 8th August 2016.

Relevant websites were searched and experts contacted. Other sources were also searched including product regulatory databases (e.g. FDA MAUDE database). Conference abstracts in published conference proceedings were searched to capture any unique safety events not reported in published full-text literature. Hand searching of reference lists of relevant studies was carried out. Clinical trials registers, including ClinicalTrials.gov and WHO ICTRP, were searched to locate any key trials which are emerging. Language filter will not be used for the searches, although non-English-language articles will be excluded unless they are thought to add substantively to the English-language evidence base. Literature search results were uploaded to and managed using EndNote X7.0.1 software.

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Database: Ovid MEDLINE(R) 1946 to June Week 5 2016

1 Aortic valve/ab (2371)

2 heart valve diseases/ or exp aortic valve stenosis/ (54586)

3 (aortic* adj stenosis).tw. (11537)

4 (valv* adj3 disease).tw. (13131)

5 or/1-4 (64515)

6 ((percutan* or transcath*) adj3 (heart* or aortic*) adj3 valve*).tw. (3802)

7 ((percutan* or transcath*) adj3 valve*).tw. (4813)

8 PAVR.tw. (36)

9 TAVR.tw. (637)

10 TAVI.tw. (1642)

11 ((transap* or transventric* or percutan* or transcath*) adj3 (deliver* or access* or approach* or minimal*)).tw. (5714)

12 animals/ not humans/ (4242300)

13 or/6-11 (10340)

14 5 and 13 (3788)

15 14 not 12 (3757)

16 limit 15 to yr="2011 -Current" (3085)

17 (201101$ or 201102$).ed. (194561)

18 16 not 17 (3069)