

evidence | *note*

Update of evidence note 52

Number 64 March 2017

Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults at high surgical risk

What is an evidence note

Evidence notes (ENs) are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions.

Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an advice statement to accompany all evidence reviews.

Please note that this evidence note is an update of evidence note 52.

Key points

- Continuing development of new transcatheter aortic valve implantation (TAVI) devices and evolving patient selection procedures mean that the published evidence base may not fully capture the outcomes associated with the latest generation of TAVI devices.
- In the PARTNER trial (cohort A), TAVI was not inferior to surgical aortic valve replacement (AVR) with respect to death from any cause after 1 year in candidates for surgery who were at high risk of operative complications and death. No difference in all-cause mortality was shown after 5 years of follow-up.
- In the CoreValve United States (US) trial, TAVI was superior to AVR with respect to mortality from any cause after 1 year and 2 years in patients at high risk of operative complications and death.
- In both the PARTNER trial and CoreValve US trial, the trial inclusion criteria to be considered high surgical risk was $\geq 15\%$ predicted risk of mortality at 30-days post AVR. However, across both studies, the mean patient the Society of Thoracic Surgeons (STS) score and the observed mortality in the AVR group was found to be below this threshold. This highlights the challenges around the interpretation of the evidence base to the

population under review.

- In the PARTNER trial (cohort A), at 1 year, TAVI was associated with a significantly higher incidence of major vascular complications and neurological adverse events including stroke. Major bleeding was less common with TAVI. At 5 year follow-up, the trend for major vascular complications and major bleeding continued, but rates of stroke became similar between the two groups.
- In the CoreValve US trial, at 1 year, TAVI was associated with significantly higher incidence of major vascular complications and permanent pacemaker implantation compared to AVR. TAVI was also associated with a lower incidence of strokes, major bleeding, acute kidney injury and new or worsening atrial fibrillation.
- A recent economic evaluation utilising the CoreValve US trial data was adapted to the NHS Scotland setting. The results indicate that TAVI may be a cost-effective treatment option for severe aortic stenosis (AS) patients at high surgical risk. However, cost-effectiveness is contingent upon the TAVI device costs being less than £19,500-£24,000 and survival benefits from TAVI being comparable to those observed in the CoreValve US trial.
- In addition to the CoreValve analysis, six previously published cost-effectiveness studies, using either PARTNER A or observational data, tended to indicate that, compared with AVR, TAVI is not a cost-effective treatment option. Two of these six previous economic evaluations suggested that TAVI may be cost effective, whilst the other four studies found TAVI may be dominated (that is, higher cost and less benefit) by AVR or associated with a high cost per quality-adjusted life year (QALY).

Definitions

Aortic stenosis (AS): an obstruction of normal blood flow across the aortic valve caused by calcification, which may have a degenerative, rheumatic or congenital aetiology.

Surgical aortic valve replacement (AVR): open-heart surgery to replace the diseased aortic valve with a mechanical prosthetic valve is the current standard treatment for patients with severe symptomatic AS who are well enough to undergo surgery.

Transcatheter aortic valve implantation (TAVI): a minimally invasive procedure in which a bioprosthetic replacement aortic valve is delivered inside a catheter, either percutaneously through the vascular system or directly through an incision in the chest.

Literature search

A systematic search of the secondary literature was carried out on 28–29 June 2016 to identify systematic reviews, health technology assessments (HTAs) and other evidence-based reports. Medline, Medline in process, Embase databases were also searched for systematic reviews and meta-analyses. Owing to the fact this evidence note is an update of a previous evidence note, results were limited to review articles published in English language between 2014 and June 2016.

The primary literature was systematically searched on 29 June 2016 using the following databases: Medline, Medline in process, Embase. The search was carried out to identify any relevant trials or observational studies. Again, results were limited to English language between 2014–June 2016.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: TAVI, transcatheter aortic valve implantation, aortic valve stenosis, aortic valve, heart valve prosthesis, heart valve prosthesis implantation. A full list of resources searched and terms used is available on request.

Introduction

This evidence note updates Evidence Note 52 published in June 2014¹. It summarises the clinical and cost-effectiveness evidence from published secondary sources, randomised controlled trials (RCTs) and economic evaluations comparing TAVI with surgical AVR in adults with severe symptomatic AS who are at high risk of surgical complications.

Epidemiology

AS is the most common native heart valve disease in adults in Europe². In most cases, the aetiology is degenerative; hence it is most often seen in the elderly, increasing with age due to degenerative calcification^{2,3}. The key diagnostic tool for AS and its severity is echocardiography⁴. Most people with mild to moderate AS are asymptomatic whereas patients with severe AS are likely to develop symptoms associated with narrowing of the valve and overload of the left ventricle, including syncope, exercise-induced angina, dyspnoea and congestive heart failure. The prevalence of severe symptomatic AS is around 3% in those aged over 75 years but this rises steeply with increasing age^{5,6}. Consequently, it is predicted that, due to an ageing population, the prevalence will increase over the following decades. The prevalence of all valvular diseases, including AS, has been predicted to double by 2046⁷. Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of 2–3 years⁶ and survival rates of only 15–50% at 5 years⁴. It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for surgical AVR^{3,8}. Patients who are not referred for surgery are more likely to be older than those who are, and more likely to have left ventricular dysfunction and multiple comorbidities³.

European guidelines recommend that TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a multidisciplinary 'heart team' based on the individual risk profile and anatomic suitability⁴.

The population prevalence of high-risk surgical patients likely to benefit sufficiently from TAVI has yet to be established^{8,9}. Projections from currently available evidence from population-based studies in Europe and the US suggested that the number of patients in the UK aged >75 years who could potentially be treated with TAVI (including inoperable and surgical high-risk) is approximately 23,838 (95% confidence interval (CI) 10,554 to 43,461)⁵. This gave an estimated 2,217 (95% CI 896 to 3,904) new potential TAVI candidates each year⁵. This would equate to approximately 220 people (95% CI 90 to 390) per year in Scotland.

Health technology description

TAVI devices and catheter systems optimised for different delivery routes have developed rapidly since the first in-man procedure was reported in 2002. The choice of implantation route depends on patient characteristics as well as the device. The most common approach is the transarterial transfemoral (TF) route in which the aortic valve is reached through the femoral artery in the groin^{9,11}. The subclavian/transaxillary, transapical (TA) and transaortic (TAo) routes have developed as alternative approaches for patients with peripheral vascular disease that precludes access via the femoral artery⁹. The subclavian/transaxillary approach involves insertion of the catheter under the collarbone to reach the aortic valve via the subclavian artery (transarterial). TA implantation requires a mini-thoracotomy to access the aortic valve through the apex of the left ventricle of the heart and hence is not strictly percutaneous. If TA implantation is not feasible, the TAo approach offers an alternative requiring a mini-thoracotomy or upper hemisternotomy to insert the delivery catheter directly into the aorta^{9,10}. Once the TAVI device compressed inside the catheter is in place within the diseased aortic valve, deployment allows it to expand into position, compressing the native diseased valve against the wall of the aorta¹⁰.

The first TAVI devices to receive the European Conformity (CE) mark, in 2007, were the balloon-expandable bovine pericardium tissue Edwards SAPIEN™ valve (Edwards Lifesciences Inc, Irving, CA, US) and the self-expanding Medtronic porcine pericardium tissue CoreValve® ReValving system for TF implantation (Medtronic, Minneapolis, MN, US)^{10,12}. In 2010, Edwards received the CE mark for the SAPIEN XT™ valve, which, like the SAPIEN™ valve, has delivery systems for TF and TA implantation. In January 2014, Edwards received the CE mark for the SAPIEN 3 valve, which can be implanted through the TF, TA and TAo routes. Medtronic received the CE mark for CoreValve TAo implantation in 2011 and for the CoreValve® Evolut™ valve in 2012, and for the Engager™ valve with a TA delivery catheter¹² in 2013. In October 2013, Boston Scientific (Boston Scientific Inc., Natick, Massachusetts, US) received the CE mark for the Lotus™ Valve System. Four other TAVI devices currently have CE mark approval (Table 1), and several more are in various stages of development^{9,11,13,14}.

Table 1: Other TAVI devices with CE mark approval

Device (Manufacturer)
Direct Flow System (Direct Flow Medical Inc., Santa Rosa, California)
JenaValve (JenaValve Technology GmbH, Munich, Germany)
Portico™ (St. Jude Medical, St. Paul, Minneapolis, US)
ACURATE TA™ (Symetis SA, Eclubens, Switzerland)

TAVI was performed for the first time in England in 2007 where a TAVI Steering Group was established in 2008 to guide introduction of the technology in the UK¹⁵. Consensus governance recommendations require a multidisciplinary team (MDT) approach to patient selection and for centres providing a TAVI service to contribute procedural, outcomes and follow-up data to the UK TAVI registry for every case^{8,15}. The UK TAVI registry recorded 3,980 TAVI cases in England and Wales between January 2007 and December 2012¹⁶.

A Scottish specialist centre for TAVI was established at the Royal Infirmary of Edinburgh (RIE) in September 2012 (N Uren, Consultant Cardiologist/Clinical Director for Cardiac Services, Royal Infirmary of Edinburgh. D Sorensen, CTR Data Manager, Royal Infirmary of Edinburgh. Personal Communication, 18 Feb 2014). The centre currently provides TAVI for patients throughout Scotland. In 2014, following the publication of Evidence Note 52, it was agreed that TAVI should not be provided for patients who, based on an MDT assessment, are suitable candidates for surgical AVR. This position has been under regular review by the NHSScotland National Planning Forum.

Patient selection

Patient selection for TAVI is largely determined by clinical judgement on an individual patient basis and should, therefore, be undertaken by an MDT including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist, and an expert in cardiac imaging^{8, 17}.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the STS-predicted risk of mortality are commonly used in the assessment of cardiac surgical risk. High risk is generally defined as a logistic EuroSCORE $\geq 20\%$ or an STS score of $\geq 10\%$ ¹¹. The ability of these scoring systems alone to accurately predict surgical risk in patients undergoing AVR, or to select patients for TAVI, is limited hence the importance of an MDT^{14, 18}.

Clinical effectiveness

9.1 Overview

Published results are available from four RCTs¹⁹⁻²² comparing TAVI with surgical AVR in high-risk operable patients – two of which are of particular relevance to the population under review^{19, 23}.

The first of these is the multicentre PARTNER trial that recruited patients at 23 sites in the US, two in Canada and one in Germany. Patients with severe calcific AS and New York Heart Association (NYHA) functional class \geq II were randomised in two separate cohorts: high-risk surgical patients were randomised to undergo TAVI with the SAPIEN™ valve or surgical AVR (cohort A) while those who were considered not to be suitable candidates for surgery were randomised to TAVI or conservative treatment in the form of medical management – usually balloon aortic valvuloplasty (BAV) (cohort B). Results for cohort A at 1 year²⁴ and 2 years²⁵, and 5 years¹⁹ of follow-up have been published.

The second RCT of interest is the multicentre US CoreValve trial²³, which recruited patients at 45 sites in the US. Patients with severe AS and heart failure symptoms of NYHA class II or higher, with a range of surgical risks, were randomised to have TAVI with the self-expanding transcatheter valve (CoreValve) or surgical AVR. Results following 1 year and 2 years of follow-up have been published.

An independent RCT, the STACCATO trial, conducted in two university hospitals in Denmark that compared TA TAVI with surgical AVR in primarily low-risk operable patients was excluded from full summary²¹. The NOTION trial, conducted in various centres across Norway, Sweden and Denmark was also excluded on the basis that the majority of the patients were low risk²².

Evidence from RCTs and a large body of matched observational trials has been collated and analysed in four relevant meta-analyses. One meta-analysis²⁶ looked exclusively at studies of TAVI versus AVR in patients with high surgical risk. Three more²⁷⁻²⁸ looked at studies of TAVI versus AVR in patients of any surgical risk. Although there was variation in baseline risks of the populations studied, the TAVI devices used and the implantation route used, on balance it was felt that the results were worth summarising in order to help identify trends and consistency across the broader TAVI indications.

The National Institute for Health and Care Excellence (NICE) updated its interventional procedure (IP) guidance on TAVI for AS in March 2012¹⁷ based on a rapid review of literature published in November 2010 that included 1-year results from the PARTNER trial, reviews of case series and case reports, registry data, and selected non-randomised comparative studies, case series and individual case reports²⁹. NICE is currently in the process of updating this IP guidance. Several technology assessments dating from publication of the PARTNER trial results have assessed the clinical effectiveness of TAVI in high-risk surgical patients. Some based their assessment solely on the PARTNER trial^{30, 31} while others also considered evidence from observational studies^{13, 31-34}. Two HTAs focused on outcomes beyond 1 year^{32, 33}.

The UK TAVI registry has published outcomes with up to 6 years follow-up for patients treated from January 2007 to December 2012¹⁶.

9.2 TAVI versus surgical AVR

9.2.1 PARTNER trial cohort A

The eligibility criteria for cohort A in the PARTNER trial included high risk of operative complications or death, defined as predicted mortality $\geq 15\%$ at 30 days and/or STS score ≥ 10 ²⁴. The primary outcome was all-cause mortality at 1 year (Kaplan-Meier analysis) in an intention-to-treat analysis of non-inferiority comparing TAVI (TF and TA) with AVR. The pre-defined margin of non-inferiority (that is, the degree of acceptable inferiority of TAVI compared with AVR) was 7.5 percentage points difference in treatment effect, and interpretation of non-inferiority was based on the upper limit of a one-sided 95% CI²⁴.

The 699 patients recruited to cohort A were categorised as being eligible for TF (n=492) or TA (n=207) TAVI and randomised in those groups to TAVI (n=244 TF, n=104 TA) or AVR (n=351). The mean age was 83.6 years (standard deviation (SD) 6.8) in the TAVI group and 84.5 years (SD 6.4) in the AVR group. The mean baseline logistic EuroSCORE was 29.3 (SD 16.5) in the TAVI group and 29.2 (SD 15.6) in the AVR group; the respective STS scores were 11.8 (SD 3.3) and 11.7 (SD 3.5). Furthermore, in relation to the criteria for high risk, it is worth noting that the observed mortality in the group receiving AVR was 6.5%.

Thirty-eight patients randomised to AVR did not undergo treatment, the main reasons being refusal and withdrawal, compared with four patients allocated to TAVI. TAVI was aborted or converted to open surgery in 16 patients (of whom nine underwent open surgery immediately and two underwent surgery more than 30 days later), and one patient allocated to AVR underwent TA TAVI²⁴.

All-cause mortality at 1 year was 24.2% in the TAVI group and 26.8% in the AVR group, a non-statistically significant difference of -2.6 percentage points (95% CI -9.3 to 4.1 ; $p=0.44$). The upper limit of the one-sided 95% CI for the treatment effect was 3.0% and within the pre-defined non-inferiority margin of 7.5% thereby demonstrating statistical non-inferiority of TAVI compared with AVR ($p=0.001$ for non-inferiority)²⁴. Patients who were eligible for TF implantation had a 1-year mortality rate of 22.2% following TAVI compared with 26.4% for AVR, which also demonstrated non-inferiority ($p=0.002$) in an adequately powered analysis²⁴. TA TAVI was not shown to be non-inferior to AVR at 1 year, but the study was not powered for this analysis²⁴.

Kaplan-Meier analysis showed no statistically significant difference between TAVI and AVR in all-cause mortality at 2 years (33.9% versus 35.0%; $p=0.78$) or over the full duration of follow up (median 727 days, maximum 1,490 days) (hazard ratio (HR)=0.90; 95% CI 0.71 to 1.15; $p=0.41$)²⁵. Regression analysis indicated that the STS score was a significant predictor of mortality at 2 years in the study cohort overall ($p=0.02$)²⁵.

TAVI was associated with a statistically significantly shorter length of index hospital stay (median 8 days versus 12 days; $p<0.001$) and stay in an intensive care unit (ICU) (median 3 days versus 5 days; $p<0.001$)²⁴.

The PARTNER trial follow-up extended to five years after the intervention. In the final report, it observed that, as for mortality data at other time points, there is no statistically significant difference in mortality (TAVI v AVR hazard ratio 1.04, 95% CI 0.86-1.24 $p=0.76$)¹⁹.

There was no statistically significant difference between TAVI and AVR with respect to repeat hospitalisation for valve or procedure-related clinical deterioration at 30 days ($p=0.64$) or 1 year ($p=0.38$)²⁴, or for heart failure, angina, or syncope symptoms due to aortic valve disease requiring aortic valve intervention or intensified medical management at 2 years ($p=0.41$)²⁵. These trends continued out to 5 years' follow-up (difference in repeat hospital admissions at 5 years $p=0.17$)¹⁹.

There was no statistically significant difference between TAVI and AVR in cardiac symptoms (NYHA functional class \leq II) or 6-minute walk test distance among evaluable patients at 1 year²⁴, or in the mean NYHA class among survivors at 2 years²⁵.

Quality of life (QoL) data were analysed separately for TF and TA implantation using intention-to-treat analysis based on patients with Kansas City Cardiomyopathy Questionnaire (KCCQ) health status scores at baseline (TAVI TF $n=230$ and TA $n=98$, surgical AVR $n=300$)³⁵. A change of five points in the KCCQ summary score corresponds with a small clinical improvement and 10 points with moderate improvement based on physician-rated assessment of outpatients with heart failure³⁵. Compared with surgical AVR, the mean KCCQ summary score (primary outcome) was significantly higher for TF TAVI at 1 month (mean difference adjusted for baseline values=9.9 points; 95% CI 4.9 to 14.9; $p<0.001$) but showed no significant difference at 6 or 12 months. For patients assigned to TA TAVI, there was a statistically significant difference in the adjusted mean KCCQ summary score in favour of AVR at 6 months (adjusted difference=-7.9 points; 95% CI -15.7 to -0.2; $p=0.04$), but no statistically significant difference at 1 or 12 months' follow-up. A similar pattern was observed in the KCCQ subscales (symptoms, physical limitation, social limitation, self-efficacy, QoL) and using the Short Form (SF)-12 and EuroQol (EQ)-5D scales³⁵.

9.2.2 CoreValve trial

The CoreValve US trial is a randomised, non-blinded, trial of TAVI using the CoreValve system (Medtronic) in patients at high surgical risk²⁰. The definition of high surgical risk that informed the eligibility criteria in this trial was a predicted risk of mortality within 30 days of $\geq 15\%$ and $< 50\%$ risk of death or serious irreversible complications at 30 days. The predicted risk of each patient was agreed by a cardiac team that included but was not limited to two cardiac surgeons and one interventional cardiologist. Additional inclusion criteria were:

- subject has senile degenerative aortic valve stenosis with mean gradient > 40 mmHg jet velocity greater than 4.0 m/s, or an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area index ≤ 0.5 cm²/m²) by resting echocardiogram, and
- subject is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.

In addition, 31 exclusion criteria were applied relating to clinical and anatomical contraindications for TAVI and AVR. Final entry to the trial was subject to the approval of the trial screening committee which occurred following recording of baseline data, including a number of prognostic investigations. 995 patients were reviewed by the screening committee and 900 patients were approved for entry to the trial.

The primary outcome of the trial was all-cause mortality at 1 year; all cause mortality at 2 years was reported in a subsequent analysis. Major secondary outcomes were:

- composite of major events, including death from any cause, myocardial infarction, any stroke, or re-intervention, at both 30 days and 1 year, and each of the individual components separately
- improvement in symptoms measured by NYHA classification, and
- QoL measured using the KCCQ and the Medical Outcomes Study 12-Item Short Form General Health Survey (SF-12).

A hierarchical statistical testing procedure was applied rather than using a multiple testing adjustment for statistical tests relating to the secondary outcomes. A difference in outcomes was only considered to be statistically significant if both the statistical test for that outcome reported significance and all previous statistical tests in the hierarchy reported statistical significance.

In total, 795 patients underwent randomisation, 394 to TAVI and 401 to AVR. More patients withdrew from the AVR group prior to the intervention than in the TAVI group (44 vs 4). This resulted in 390 patients undergoing attempted TAVI and 357 patients undergoing attempted AVR. Of these patients, 389 had successful TAVI procedure and 353 had successful AVR procedure. It should be noted that, although the trial eligibility criteria indicated that patients should be at $\geq 15\%$ risk of mortality or serious irreversible morbidity within 30-days of surgery, the observed 30-day mortality rate in the AVR arm of the trial was only 4.5%. This raises concerns over whether the patients recruited to the trial truly represent the high surgical risk population. Patients had lower observed operative mortality than was anticipated; however, the trial clearly defined a patient selection process aiming to select high-risk patients.

Mortality at 1 year was lower in the group randomised to TAVI (13.9%) compared with the group randomised to AVR (18.7%) ($p=0.04$). Very similar results were reported in an as-treated analysis (14.2% vs 19.1%, $p=0.04$)²⁰. Reported mortality at 2 years showed continuing benefit for TAVI compared to AVR in an as-treated analysis (22.2% vs 28.6%, $p<0.05$)³⁶.

The composite major event rate at 30 days was 8.2% in the TAVI group compared to 10.9% in the AVR group ($p=0.10$). At 1 year, the major event rates were lower for TAVI²⁰ (20.4% vs 27.3%, $p=0.03$) and this persisted at 2-years (29.7% vs 38.6%, $p=0.01$)³⁶. Change from baseline to 1 year follow-up NYHA classification showed no difference between TAVI (1.46) and AVR (1.46). There was also little difference in the change in KCCQ at 1 year follow-up (TAVI: 23.2, AVR 28.8). Change in quality of life at 1-year, as measured by SF-12, was more positive for TAVI (+4.91 vs -0.12); however, this was not statistically significant under the hierarchical testing procedure²⁰.

9.2.3 Secondary evidence

9.2.3.1. Meta-analysis high surgical risk

One network meta-analysis included only the high surgical risk group of patients²⁶. This analysis only included RCTs that compared treatment of severe aortic stenosis with TAVI (that is, one of the following methods of delivery; SAPIEN-TA, SAPIEN-TF, or CoreValve) versus surgical AVR. Four studies were identified and used in the analysis: the CHOICE, PARTNER cohort A, STACCATO

(selected high risk patient), and US CoreValve studies. Results were reported for each TAVI method of delivery versus AVR.

This meta-analysis incorporated most of the relevant RCTs, but did not include data from the longer follow-up of the PARTNER trial and a number of matched observational trials - many of which may have been relevant.

For 1-year mortality, none of the TAVI methods showed a statistically significant improvement versus AVR. For one procedure, SAPIEN-TA, the analysis found a non-statistically significant worsening in mortality, while for the other two it showed a non-statistically significant improvement. (Odds ratio vs AVR and 95% CI: CoreValve 0.72, 0.50-1.05; SAPIEN-TF 0.82, 0.55-1.23; SAPIEN-TA 1.35, 0.47-2.38)²⁶.

No statistically significant difference was found in rates of stroke (CoreValve OR 0.70, 95% CI 0.44-1.06; SAPIEN-TF OR 2.20, 95% CI 0.95-5.34; SAPIEN-TA 2.12, 95% CI 0.80-6.08), or rates of myocardial infarction (CoreValve OR 1.27, 95% CI 0.39-4.33; SAPIEN-TF OR 2.50, 95% CI 0.20-67.41; SAPIEN-TA OR 0.65, 95% CI 0.09-4.17)²⁶.

For acute kidney injury post procedure, the analysis found an improvement when using TAVI (CoreValve OR 0.48, 95% CI 0.30-0.75; SAPIEN-TF OR 0.72, 95% CI 0.35-1.52; SAPIEN-TA OR 0.36, 95% CI 0.01-4.52). However, TAVI was found to worsen rates for permanent pacemaker insertion (CoreValve OR 2.46, 95% CI 1.69-3.61; SAPIEN-TF OR 1.11, 95% CI 0.62-2.04; SAPIEN-TA 1.05, 95% CI 0.36-2.95) and moderate/severe aortic regurgitation (CoreValve OR 15.91, 95% CI 3.76-123.10; SAPIEN [reported together] OR 5.91, 95% CI 1.31-57.38)²⁶.

Overall, TAVI, compared to AVR, led to no statistically significant difference in mortality, a significant reduction in major bleeding and acute kidney injury, but a worsening in permanent pacemaker insertion and aortic regurgitation²⁶.

9.2.3.2. Meta-analysis any surgical risk (including high risk)

Three meta-analyses examined all patients regardless of surgical risk²⁷⁻²⁸. One analysis looked at all patients in the base case and patients with low-intermediate surgical risk in a subgroup analysis, but did not present the high surgical risk subgroup²⁷. The other two analyses did not consider surgical risk at all^{37, 28}.

All three studies were published in 2016, and included matched observational studies as well as RCTs. Owing to the fact these analyses included patients at low and intermediate surgical risk, their applicability to this evidence note on high risk patients is limited. These analyses include patients who were not high surgical risk. As a description in Gargiulo et al notes, most patients in the NOTION trial were low risk, the PARTNER 2A trial was on intermediate risk patients only, and 6 of its 31 matched studies included patients at low to intermediate risk. Other analyses similarly included studies with low and intermediate risk patients. However, all three were published in 2016, making them the most recent meta-analyses. Further, all three included matched observational studies, whereas Biondi-Zoccai et al was limited to RCTs.

On mortality, Gargiulo et al and Cao et al reported on mortality from any cause at 30 days, 1 year, and 'long-term' or 'beyond 12 months'^{27, 37}. At all time points and in both analyses, no statistically significant difference was found. (Odds ratio vs AVR and 95% CI at 30 days: Gargiulo,

1.01, 0.81-1.26; Cao 1.06, 0.83-1.34. At 1 year: Gargiulo 0.96, 0.81-1.26; Cao 0.95, 0.70-1.27. Long-term: Gargiulo 1.28, 0.97-1.69; Cao 1.13, 0.89-1.44). By contrast, Takagi et al reported a statistically significant worsening in the hazard ratio for mortality (hazard ratio 1.21, 95% CI 1.05-1.39).

Rates of stroke were not found to be statistically significant, and the two analyses differed in the direction of the base value (Gargiulo: early 0.84, 0.64-1.09; midterm 0.92, 0.62-1.35. Cao: during periprocedural period 1.01, 0.72-1.43; at 12 months 1.10, 0.68-1.78; beyond 12 months 1.44, 0.82-2.53)^{27, 37}.

Both studies reported that TAVI improved rates of myocardial infarction, with Gargiulo showing statistical significance (Gargiulo 0.51, 0.38-0.69; Cao 0.76, 0.33-1.75). This was also the case for acute kidney injury (Gargiulo 0.50, 0.34-0.73; Cao 0.96, 0.55-1.67) and new-onset atrial fibrillation (Gargiulo 0.24, 0.15-0.40, not reported in Cao).

Both studies reported on vascular complications and found that TAVI worsens these significantly (Gargiulo 4.32, 1.82-10.3; Cao 4.62, 2.90-7.37). The studies also found TAVI led to worse rates of permanent pacemaker insertion (Gargiulo 2.32, 1.62-3.31; Cao 2.65, 1.66-4.24) and paravalvular leak (Gargiulo 6.66, 5.26-8.45; not reported in Cao).

Overall, these three analyses give differing reports on mortality, with two showing no statistically significant difference (albeit often trending to a worse result for TAVI) and one reporting a statistically significant worsening. All show an improvement in major bleeding rates. TAVI is reported to lead to greater vascular complications, more permanent pacemaker insertions, and more paravalvular leaks, but may improve rates of myocardial infarction and acute kidney injury.

9.2.3.3. Other secondary sources

In 2012, NICE concluded that the evidence on the efficacy of TAVI for patients who are suitable for surgical AVR but at high risk was inadequate, and that TAVI should only be used with special arrangements for clinical governance, consent and data collection or research¹⁷. In the case of patients suitable for surgical AVR who are not at high risk, the evidence was again inadequate and TAVI should only be used in the context of research. NICE is currently in the process of updating this IP guidance.

The results from the PARTNER trial cohort A have been reported in several technology assessments concluding that TAVI and surgical AVR resulted in similar survival and functional outcomes^{13, 30-34}. The Technology Assessment Unit of the McGill University Health Centre (MUHC) assessed outcomes at 2 years and beyond based on the PARTNER trial and observational studies (including UK and SOURCE registry data) published to January 2013, and concluded that survival rates for TAVI and AVR were comparable³³. The Canadian Agency for Drugs and Technologies in Health (CADTH) assessment of clinical effectiveness beyond 12 months also concluded that TAVI and surgical AVR yielded similar clinical outcomes³². Australia's HealthPACT reviewed TAVI largely based on data from use in Australia and New Zealand practice.³⁸ This work included a report of an estimate of the benefit-risk balance of CoreValve versus AVR, which said that for every 1,000 patients treated, benefits included preventing 49 deaths, 72 major bleeding events and 38 strokes among other gains, but at the cost of 110 extra pacemaker implantations and 42 more major vascular events. It concluded that TAVI "remains a controversial technology with significant potential to influence the

management of patients with both inoperable and operable aortic valve disease and to impact significantly on health budgets”³⁸.

9.3 TAVI registry data

The UK TAVI registry reported trends and outcome data for 3,980 TAVI procedures performed at 33 centres across the UK from 2007 to 2012¹⁶. The majority of patients received either the SAPIEN/SAPIEN XT valve (n=2,036) or the CoreValve (n=1,897), with 71.2% of procedures performed via femoral access.¹⁶ Data from 1,620 patients treated to December 2010 showed 97.4% TF implantation success with the SAPIEN valve and 95.7% with CoreValve; and 97.3% for TA (SAPIEN) and 95.7% success for subclavian (CoreValve) implantation³⁹.

The UK TAVI registry (2007–2012) reported 81.7% survival at 1 year, 72.8% at 2 years, 46.9% at 5 years and 37.3% at 6 years. There was no difference in survival at any time point between SAPIEN and CoreValve devices. There was an observed trend towards higher survival in the more recent TAVR cohorts. The 4-year survival was 55% for those treated in 2009 and 65% for those treated in 2011. Furthermore, survival at 1, 2 and 3 years was higher for patients treated in 2012 than for those treated in all previous years. It is worth noting that in an attempt to address a possible issue of a learning curve, the first 50 cases at each centre were compared with the subsequent cases, with no difference in 30-day mortality found¹⁶.

Median post-procedural length of stay was 8 days (interquartile range, 6-13 days), with a decrease from 10 days over the study period. The percentage of patients discharged on the third day post procedure remained stable at 5.6%, yet the percentage of patients who could be discharged after five days increased from 16.7% in 2007 to 28.5% in 2012¹⁶.

Safety

10.1 PARTNER trial cohort A

The trial found no statistically significant reduction in all-cause mortality at 30 days in the TAVI group compared with AVR by intention-to-treat (3.4% versus 6.5%; p=0.07) or in the as-treated analysis (5.2% versus 8.0%; p=0.15)²⁴. Patients who were eligible for TF implantation had a 30-day mortality rate of 3.3% following TAVI compared with 6.2% for AVR (p=0.13) (3.7% and 8.2% as-treated, p=0.046). The rates for patients stratified to receive TA implantation were 3.8% and 7.0% (p=0.32) (8.7% and 7.6% as-treated, p=0.79)²⁴. All-cause mortality at five years was also not statistically significant (67.8% versus 62.4%, p=0.76)¹⁹.

Multiple (≥2) transcatheter valves were implanted in seven patients (0.2%) due to residual aortic regurgitation (five patients) or valve embolisation (two patients)²⁴. Seven other patients who experienced valve embolisation underwent conversion to AVR (five patients) or had transcatheter placement aborted (two patients)²⁴.

Major vascular complications were significantly more common in the TAVI group compared with AVR at 30 days (11.0% versus 3.2%; p<0.001), 1 year (11.3% versus 3.5%; p<0.001)²⁴, 2 years (11.6% versus 3.8%; p<0.001)²⁵, and 5 years (11.9% versus 4.7%, p=0.0002)¹⁹.

Neurological adverse events – stroke and transient ischaemic attack (TIA) – were more common in the TAVI group at 30 days (5.5% versus 2.4%; p=0.04), 1 year (8.3% versus 4.3%, p=0.04)²⁴ and 2 years (11.2% versus 6.5%; p=0.05)²⁵, but not at 5 years (15.9% versus 14.7%, p=0.35)¹⁹. The

rate of major strokes was 3.8% in the TAVI group versus 2.1% in the AVR group at 30 days ($p=0.20$) 5.1% versus 2.4% at 1 year ($p=0.07$)²⁴. Kaplan-Meier analysis showed no statistically significant difference in the number of all strokes at 2-year follow-up between TAVI and AVR (7.7% versus 4.9%; $p=0.17$) or at 5 years (10.4% versus 11.3%, $p=0.61$)¹⁹. A post-hoc analysis of all neurological adverse events (34 strokes and 15 TIA in 31 TAVI and 16 AVR patients) showed a peak in the risk of adverse events in the first week in both groups but higher for TAVI. The risk then declined to a constant hazard in both groups up to 2 years' follow-up during which the likelihood of neurological events following either treatment was associated with patient-related factors including non-eligibility for TF implantation, recent history of stroke or TIA and greater functional disability⁴⁰.

Major bleeding was significantly more common with AVR than with TAVI at 30 days (19.5% versus 9.3%; $p<0.001$), 1 year (25.7% versus 14.7%; $p<0.001$)²⁴, 2 years (29.5% versus 19.0%; $p=0.002$)²⁵ and 5 years (26.6% versus 34.4%, $p=0.003$)¹⁹.

There was no statistically significant difference between TAVI and AVR in the number of patients requiring a new pacemaker at 30 days (3.8% in the TAVI group, 3.6% in the AVR group)²⁴, 1 year (5.7% TAVI, 5.0% AVR)²⁴, 2 years (7.2% TAVI, 6.4% AVR)²⁵ or 5 years (9.7% TAVI, 9.1% AVR)¹⁹. There was also no statistically significant difference in rates of myocardial infarction at 30 days, 1 year, 2 years or 5 years^{19, 24, 25}, acute kidney injury at 30 days or 1 year²⁴, or renal failure at 2 years²⁵ or 5 years¹⁹.

There were no cases of structural valve deterioration requiring surgical replacement in either group after 2 years, although the investigators noted that definitive assessment of valve durability required much longer follow-up²⁵.

10.2 CoreValve trial

All-cause mortality at 30 days, as used in the definition of high surgical risk, was similar for TAVI (3.3%, $n=13$) and AVR groups (4.5%, $n=16$) ($p=0.43$). Rates of major stroke at 30 days were also similar; 3.9% ($n=15$) for TAVI and 3.1% ($n=11$) for AVR ($p=0.55$). Three patients in the TAVI group received a re-intervention by 30 days compared to none in the AVR group ($p=0.1$)²⁰.

Neurovascular adverse event rates were similar for TAVI and AVR at 30 days (4.9% vs 6.2%, $p=0.46$) but diverged at later time points. The frequency of all stroke was higher for AVR compared to TAVI at 1 year (8.8% vs 12.6%, $p=0.10$) and 2 years (10.9% vs 16.6%, $p=0.05$)^{20, 36}.

Major vascular complications were significantly more common in the TAVI group (1 year: 6.2% vs 2%, $p=0.004$).

Bleeding events reported at 1-year follow-up were significantly more common in the AVR group; life-threatening or disabling bleeding 16.6% vs 38.4% ($p<0.001$), major bleeding 29.5% vs 36.7% ($p=0.03$).

Acute kidney injury was likewise significantly more common in the AVR group at 1-year follow-up (6% vs 15.1%, $p<0.001$).

New onset or worsening atrial fibrillation was significantly more likely in the AVR group at 1-year follow-up (15.9% vs 32.7%, $p<0.001$).

The rate of permanent pacemaker implantation was significantly higher in the TAVI group at 1-year follow-up (22.3% vs 11.3%, $p < 0.001$).

Cardiac perforation occurred in five patients receiving TAVI and none receiving AVR.

At the latest follow-up point of 2 years, no evidence was found of structural valve deterioration. The authors stated that this issue will require longer follow-up to provide a definitive comparison between TAVI and AVR³⁶.

10.3 Secondary evidence

10.3.1. Meta-analysis high surgical risk

In the only meta-analysis exclusively for high risk patients, for 1-year mortality, none of the TAVI methods showed a statistically significant improvement vs AVR (odds ratio vs AVR and 95% CI: CoreValve 0.72, 0.50-1.05; SAPIEN-TF 0.82, 0.55-1.23; SAPIEN-TA 1.35, 0.47-2.38)²⁶.

The analysis did find a statistically significant improvement in reducing major bleeding events for all TAVI methods vs AVR. (CoreValve OR 0.33, 95% CI 0.24-0.45; SAPIEN-TF OR 0.55, 95% CI 0.37-0.83; SAPIEN-TA OR 0.48, 95% CI 0.27-0.83.)²⁶

TAVI was found to worsen rates for permanent pacemaker insertion (CoreValve OR 2.46, 95% CI 1.69-3.61; SAPIEN-TF OR 1.11, 95% CI 0.62-2.04; SAPIEN-TA 1.05, 95% CI 0.36-2.95) and moderate/severe aortic regurgitation (CoreValve OR 15.91, 95% CI 3.76-123.10; SAPIEN [reported together] OR 5.91, 95% CI 1.31-57.38).²⁶

No statistically significant difference was found in rates of stroke (CoreValve OR 0.70, 95% CI 0.44-1.06; SAPIEN-TF OR 2.20, 95% CI 0.95-5.34; SAPIEN-TA 2.12, 95% CI 0.80-6.08), or rates of myocardial infarction (CoreValve OR 1.24, 95% CI 0.39-4.33; SAPIEN-TF OR 2.50, 95% CI 0.20-67.41; SAPIEN-TA OR 0.65, 95% CI 0.09-4.17)²⁶.

10.3.2. Meta-analysis any surgical risk (including high risk)

As noted in 9.2.3, these meta-analyses looked at patients with any surgical risk, which means that data reported here may indicate trends in safety but may not be representative of the high surgical risk group.

On mortality, Gargiulo et al and Cao et al reported on mortality from any cause at 30 days, 1 year, and 'long-term' or 'beyond 12 months'. At all time points and in both analyses, no statistically significant difference was found. (Odds ratio vs AVR and 95% CI at 30 days: Gargiulo, 1.01, 0.81-1.26; Cao 1.06, 0.83-1.34. At 1 year: Gargiulo 0.96, 0.81-1.26; Cao 0.95, 0.70-1.27. Long-term: Gargiulo 1.28, 0.97-1.69; Cao 1.13, 0.89-1.44.) By contrast, Takagi et al reported a statistically significant worsening in the hazard ratio for mortality (hazard ratio 1.21, 95% CI 1.05-1.39).

Other outcomes are only reported by Gargiulo et al and Cao et al. Both found a statistically significant improvement in major bleeding under TAVI (Gargiulo OR 0.49, 95% CI 0.26-0.95; Cao 0.49, 95% CI 0.37-0.67). Rates of stroke were not found to be statistically significant, and the two analyses differ in the direction of the base value (Gargiulo: early 0.84, 0.64-1.09; midterm 0.92,

0.62-1.35. Cao: during periprocedural period 1.01, 0.72-1.43; at 12 months 1.10, 0.68-1.78; beyond 12 months 1.44, 0.82-2.53).

Both studies reported that TAVI improved rates of myocardial infarction, with Gargiulo showing statistical significance (Gargiulo 0.51, 0.38-0.69; Cao 0.76, 0.33-1.75). This was also the case for acute kidney injury (Gargiulo 0.50, 0.34-0.73; Cao 0.96, 0.55-1.67) and new-onset atrial fibrillation (Gargiulo 0.24, 0.15-0.40, not reported in Cao).

Both studies reported on vascular complications and found that TAVI worsens these significantly (Gargiulo 4.32, 1.82-10.3; Cao 4.62, 2.90-7.37). The studies also found TAVI led to worse rates of permanent pacemaker insertion (Gargiulo 2.32, 1.62-3.31; Cao 2.65, 1.66-4.24) and paravalvular leak (Gargiulo 6.66, 5.26-8.45; not reported in Cao).

10.3.3. Other secondary sources

NICE IP guidance states that evidence on the safety of TAVI shows the potential for serious but well-recognised complications¹⁷. It recommends that units undertaking TAVI should have cardiac and vascular surgical support for emergency treatment of complications, and clinicians should ensure that patients understand the risk of stroke and death, and the uncertainty about the procedure's long-term efficacy¹⁷. NICE recommended that further research should include as outcomes the incidence of stroke and other adverse events, aortic regurgitation and valve durability as well as symptom relief and QoL¹⁷. NICE is currently in the process of updating this IP guidance.

HTAs corroborated the evidence of increased risk of serious adverse events associated with TAVI, including major vascular complications and neurological events, and, compared with surgical AVR, an increased risk of paravalvular regurgitation^{13, 30-34}.

10.4 TAVI registry data

The UK TAVI registry reported 6.3% mortality at 30 days for the whole cohort. 30-day mortality was highest in 2007 and 2008 (9.7%) and decreased to between 5.4% and 6.3% between the years 2009–2012¹⁶.

Post-procedural (≤ 30 days) major vascular complications affected 6.3% of patients in the UK TAVI registry (2007–2009) and were more common following TF implantation compared with other routes (8.4% vs 1.9%; $p < 0.001$)⁴¹. This overall figure fell to 2.6% in 2012¹⁶. There was no difference between SAPIEN and CoreValve devices.

The incidence of procedure-related stroke (≤ 30 days) was 4.1% in the UK TAVI registry (with no statistically significant difference between TF and other routes, or between SAPIEN and CoreValve devices)⁴¹. This figure fell to 2.4% in 2012¹⁶.

Post-procedural (≤ 30 days) moderate to severe (grade > 2) paravalvular regurgitation was reported in 13.5% of patients in the UK TAVI registry, and was significantly more common in the TF group compared with other routes (15.6% vs 9.1%; $p = 0.01$) and with CoreValve compared with SAPIEN devices (17.3% vs 9.6%; $p = 0.001$)⁴¹. The UK registry (2007–2010) showed rates of aortic regurgitation assessed by echocardiography immediately post procedure of 8.0% (TF) and 6.1% (TA) for SAPIEN devices, and 13.5% (TF) and 8.5% (subclavian) for CoreValve³⁹.

New permanent pacemaker implantation was required within 30 days by 7.4% of SAPIEN and 24.4% of CoreValve recipients recorded in the UK registry ($p < 0.001$)⁴¹, with the respective figures falling to 5.8% and 14.5% in 2012¹⁶.

The long-term durability of bioprosthetic percutaneous prosthetic valves, which are susceptible to degeneration, calcification and inflammation, is of particular concern when the indication for TAVI extends to patients with longer life expectancy^{9, 11, 42}. Published registry data lack sufficient follow-up or data to provide useful information on the longer term durability of TAVI devices.

Ongoing RCTs

Ongoing RCTs comparing TAVI with surgical AVR are summarised in Table 2. NICE encourages clinicians to enter all suitable patients into the UK TAVI trial, a National Institute for Health Research (NIHR) sponsored multicentre non-inferiority trial comparing TAVI with surgical AVR in patients with severe symptomatic AS who are at high or intermediate surgical risk¹⁷.

Table 2: Ongoing RCTs comparing TAVI with surgical AVR

Study	Status	Participants	Intervention	Comparator	Primary outcome	Estimated completion
UK TAVI Sponsor: NIHR	Recruiting Estimated enrolment n=808	Symptomatic severe AS, high or intermediate risk	TAVI (any CE-marked device and any approach in current use)	Surgical AVR	All-cause mortality at 1 year (non-inferiority); up to 7.5% in favour of AVR	Publication date August 2018
PARTNER trial NCT00530894 Sponsor: Edwards Lifesciences	Ongoing, but not recruiting Estimated enrolment n=3,285	Symptomatic severe AS, high-risk (Cohort A) or inoperable (Cohort B)	Edwards SAPIEN™; Cohort A high risk (TF or TA); Cohort B inoperable (TF)	Surgical AVR (Cohort A) or medical management and/or BAV (Cohort B)	Freedom from death at 1 year (Cohort A) or at duration of study (Cohort B)	March 2017 Primary outcome: completed
PARTNER II NCT01314313 Sponsor: Edwards Lifesciences	Ongoing, but not recruiting Enrolment n=2,032	Symptomatic severe AS	Edwards SAPIEN XT™; delivery system NovaFlex (TF) or Ascendra2 (TA)	Surgical AVR	Time to death, major stroke and repeat hospitalisations at 2 years; composite of all-cause mortality and major stroke	May 2018 Primary outcome: completed
US CoreValve high risk study NCT01240902 Sponsor: Medtronic Cardiovascular	Ongoing, but not recruiting Enrolment n=795	Symptomatic severe AS, high risk	Medtronic CoreValve® System (TF or trans-subclavian)	Surgical AVR	All-cause mortality at 12 months	November 2017 Primary outcome: completed
SURTA VI NCT01586910 Sponsor: Medtronic Cardiovascular	Recruiting Estimated enrolment n=2,500	Symptomatic AS, intermediate risk	Medtronic CoreValve® System (TF or trans-subclavian)	Surgical AVR	All-cause mortality or disabling stroke at 24 months	Data collection for primary outcome: October 2016

NOTION (Nordic aortic valve intervention trial) NCT01057173 Sponsor: Rigshospitalet, Denmark	Ongoing, but not recruiting Estimated enrolment n=280	Severe AS, eligible for TAVI and surgical AVR	Medtronic CoreValve [®] System (TF or trans-subclavian)	Surgical AVR	Composite of death from any cause, MI and stroke at 1 year	April 2018 Primary outcome: April 2014
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Cost effectiveness

Seven economic evaluations have assessed the cost effectiveness of TAVI for high-risk surgical patients with AS who are eligible for conventional AVR surgery. Two of the seven studies were carried out from a UK perspective^{43,44}, one from a Belgian perspective⁴⁵, while the remaining four are from North America^{23,46-48}.

The economic evaluations can further be grouped by the key source of the clinical-effectiveness evidence used to underpin the evaluation. One study was based on the most recent CoreValve US trial²³, five studies used the PARTNER cohort A results and a single study used neither CoreValve US nor PARTNER cohort A trial results.

The most recent economic evaluation, Reynolds et al (2016), reported a cost-utility analysis. The lifetime horizon (20 years) was used with a discount rate of 3% applied to both costs and health benefits. CoreValve US trial data alone were used to estimate survival, resource use, and health-related QoL (EQ-5D) for both TAVI and AVR for the initial period of 24 months. A cohort Markov model was used to synthesize the costs and outcomes data and also provide extrapolation to the lifetime horizon. A key assumption of the model is that the hazard ratio for mortality for severe AS patients relative to the general population, for the period following 24 months until the lifetime horizon, is constant and the same for both TAVI and AVR patients. This may be a conservative assumption as it implies no further benefit from TAVI on mortality beyond 24 months; however, it also implies no increased mortality from longer-term adverse events following TAVI. In terms of QoL measurement, EQ-5D data were valued using US reference weights which are somewhat different to UK reference weights and may result in higher or lower estimates of QALYs. Beyond the initial 24 months, QoL was assumed to be the same for TAVI and AVR patients.

Index admission costs were calculated by multiplying resource use data gathered across all study sites, including device costs, surgical procedure costs and hospital stay, by unit costs estimated at two study sites. Some additional index admission, follow-up and adverse event costs were estimated based on hospital billing data from all study sites. Disaggregated resource use and unit cost estimates were not presented in full. TAVI device costs were assumed to be \$32,000 (£26,240). All medical costs, including those not related to severe AS were included in the analysis. Unit costs will be different in the Scottish context and resource use may also differ. Unrelated medical costs are not usually included in economic evaluations in the UK context.

The base case results of the model reported an ICER of \$55,090 (£45,174), based on 0.324 incremental QALYs and incremental costs of \$17,849 (£14,636). In a scenario analysis in which lifetime unrelated medical costs were excluded (consistent with UK base case for economic evaluations), the reported ICER reduced to \$32,728 (£26,837). Sub-group analysis suggested that there may be important differences between male (ICER: \$99,459 (£81,556)) and female (ICER: \$49,145 (£40,299)) patients and those with a lower risk of operative mortality, STS PROM score <7 (ICER: \$49,656 (£40,718)), compared to those with a higher a higher risk of operative mortality, STS PROM score ≥7 (ICER: \$225,250 (£184,705)). No important difference was identified between transfemoral access (ICER: \$52,897 (£43,376)) and non-transfemoral access (ICER: \$62,767 (£51,469)) groups. Note that the sub-group analyses have high uncertainty because the CoreValve US trial on which the evaluation is based was only adequately powered for the overall comparison between TAVI and AVR. Results were not sensitive to the discount rate or assumptions about long-term health benefits. TAVI index admission costs, which includes device costs, were a key driver of cost effectiveness (the ICER reduced by \$3,000 for each \$1,000 reduction in TAVI index admission costs) although other costs were not.

The US context adopted by Reynolds et al means that the results may not be directly applicable to NHSScotland. To understand how results change if an NHSScotland context is adopted, an adaptation of the original economic evaluation was produced (*SHTG, companion publication*). The economic model was first recreated and then key cost parameters and selected other parameters were repopulated using more appropriate estimates given the Scottish context. Additional simplifying assumptions were used to produce the adapted model. An important assumption was made that although specific resource use differed, the total cost of future healthcare resource use, including that related to adverse events, were identical for TAVI and AVR. This was considered justified on the basis of total costs reported in Reynolds et al. Further details of the adaptation methods are available in the SHTG companion publication for this evidence note. TAVI cost estimates were provided by NHS Lothian based on the tariff charged per TAVI procedure. AVR cost estimates were based on a Scottish national tariff. Alternative cost estimates were explored in a sensitivity analysis.

In the model adaptation base case the [REDACTED] (without discounts: £23,089), based on 0.40 incremental QALYs and incremental costs of [REDACTED] (without discounts: £9,647).¹ A key driver of cost effectiveness was the index admission costs for TAVI – where a major contributor to the index admission cost was the TAVI device cost. Threshold analysis demonstrated that TAVI device costs of up to £24,000 were associated with ICERs below £30,000 and device costs of up to £19,500 were associated with ICERs below £20,000. Two-year mortality results are also key drivers of the model, whereas results are relatively insensitive to variation in the longer-term mortality estimates and other costs. The difference in 2-year mortality at which TAVI becomes cost-effective at a £30,000 ICER threshold is 3.3 percentage points (TAVI 25.3% vs AVR 28.6%). At a £20,000 threshold, the difference at which TAVI becomes cost-effective is 5.4 percentage points (TAVI 23.2% vs AVR 28.6%), the base case difference was 6.4 percentage points. Results of the model adaptation should be interpreted with consideration of the limitations of the original evaluation and the additional simplifying assumptions imposed in the adaptation process.

The UK study carried out by Fairbairn *et al* (2013)⁴³ presented a cost-utility analysis in the form of a Markov model with a 10-year time horizon. The clinical evidence for the model was based on the results of the PARTNER trial cohort A which was the only randomised trial of TAVI versus AVR in high-risk patients available at the time. With the results of PARTNER cohort A in mind – where there was found to be no significant difference between TAVI and AVR for a number of the key endpoints – it was unsurprising to find that the economic model estimated very little difference in the number of quality-adjusted life years (QALYs) generated by each procedure. Over the 10-year time horizon, TAVI was estimated to generate 2.81 QALYs compared with 2.75 QALYs for AVR, a difference of 0.06 QALYs.

The key aspect of the Fairbairn *et al*⁴³ study concerned the relative costs of the two interventions. Despite the higher procedural costs associated with TAVI (£16,500 vs £9,256 for TAVI and AVR respectively), the results of the economic evaluation showed that TAVI dominated AVR (that is, TAVI generates more QALYs and is associated with a lower overall cost). This result stemmed from the fact that AVR post-surgical procedural costs – based largely on length and cost of hospital stay – were estimated to be much greater than TAVI post-surgical costs. The assumption surrounding length of stay in the economic model is one of the few model inputs that is not consistent with the results of PARTNER cohort A. Although this may be an attempt to reflect UK practice, the assumptions should be treated with caution. For example, in the model, AVR is assumed to be associated with a 5-day stay in intensive care, compared with 0.5 days for TAVI. The results of PARTNER cohort A show the median lengths of

¹ Redacted as commercial in confidence data.

stay to be 5 days for AVR, but 3 days for TAVI. As shown in the Fairbairn *et al* sensitivity analysis, incorporating a 3-day stay in intensive care for TAVI means that TAVI no longer dominates and is associated with a cost per QALY of £32,660.

The findings of the Fairbairn study highlight the sensitivity of cost effectiveness results to even small changes to the costs assumptions – both TAVI device costs and length of stay comparisons between the two procedures.

A second UK study⁴⁴ also included a model to assess the cost effectiveness of TAVI compared with AVR. A Markov model was built which incorporated a 25-year (lifetime) time horizon.

The base case results presented by Orlando *et al*⁴⁴ show that TAVI is both more costly and less effective (in terms of QALYs) than AVR. This base case result is shown to be robust to a variety of changes to the assumptions regarding the relative effectiveness of the treatments. This leads the authors to suggest that TAVI should not be widely used as an alternative to AVR.

There are a number of limitations with this analysis. The key weakness is that the model inputs are not based on randomised data, and it is not clear which data were included in the model. Although the study by Orlando *et al* was published in 2013⁴⁴, the modelling was said to be undertaken before March 2011 and prior to the publication of the PARTNER cohort A trial results. This significant weakness surrounding the model inputs translates to weakness in the model outputs, and therefore the results of this model must be treated with caution.

A Belgian study⁴⁵ also used a Markov model to assess the cost effectiveness of TAVI for the high-risk patient group. The clinical evidence used to populate the economic model was drawn from the PARTNER trial cohort A, which meant that TAVI was associated with only a small QALY gain (0.03) vs AVR. Combining the QALY gain with an estimated incremental TAVI cost of €20,400 (£17,128) resulted in an overall cost per QALY of €750,000 (£629,691). A contributing factor to the high cost per QALY is the twice as high rate of stroke after TAVI compared with surgery (8.3% vs 4.3% at year 1). Owing to the fact that the PARTNER results for high-risk patients (cohort A) did not show significant survival differences after 1 year, the model's time horizon was restricted to the 1-year trial follow-up period.

Neyt *et al*⁴⁵ conclude that TAVI is not cost-effective for the high-risk patient group, with the less invasive nature of the TAVI procedure not, by itself, sufficient to justify the extra costs. It should be noted, however, that this conclusion can be altered if, for example, TAVI costs were to become similar to those of AVR. Consideration may also be given to the fact that the costs for each treatment arm within Neyt *et al*'s analysis were derived from different time periods, and therefore the results may be confounded.

The three North American economic evaluations were populated using PARTNER cohort A data. Each study found TAVI and AVR to be associated with similarly small QALY changes. However, the two US studies (Reynolds *et al*, 2012⁴⁸ and Gada *et al*, 2012⁴⁶) presented very similar costs for the two treatment arms, while the Canadian study⁴⁷ found TAVI to be associated with a much greater cost than AVR. As such, results from the studies differed markedly. In the two US studies, Reynolds *et al* (2012) produced an ICER of \$76,877 (£46,471) while Gada *et al* reported an ICER of \$52,773 (£32,089). In the Canadian economic evaluation of Doble *et al*, TAVI was found to be dominated by AVR. TAVI was associated with an additional cost of \$11,153 (£6,782) and was found to produce 0.10 fewer QALYs.

12.1 Summary of cost effectiveness

The results of the seven economic evaluations assessing the cost effectiveness of TAVI compared with conventional AVR surgery reported a wide range of cost-effectiveness results. The six evaluations conducted prior to the US CoreValve trial tended to indicate that TAVI may not be a cost-effective option for the high-risk AS patient group. Two of the six studies – at least for the TF access route – demonstrated that TAVI may be cost-effective, while the other four studies found that TAVI may be either dominated by AVR or associated with a high cost per QALY. The single economic evaluation available using the US CoreValve trial data indicated that TAVI compared with AVR may be a cost-effective option. An adaption of this evaluation from the US context to the Scottish context demonstrated that TAVI may be cost-effective in this indication in NHSScotland provided the TAVI device costs are less than £19,500–£24,000.

Differences between the earlier economic evaluations and between these evaluations and the US CoreValve evaluation are explained by the importance of the US CoreValve trial in changing the estimate of effect of TAVI on survival outcomes. Prior to the US CoreValve trial, the outcomes associated with TAVI and AVR appeared to be similar, and consequently the focus within the economic evaluations tends to turn to the relative costs of the interventions. The additional procedural cost, largely due to higher device cost associated with TAVI, does not appear to be offset by reductions in other healthcare costs, which leads to the conclusion that TAVI does not appear to be cost-effective for this patient group if outcomes are similar. Based on the latest evidence from the CoreValve US trial, outcomes for TAVI are superior to those for AVR. The estimated additional health benefits may justify the additional costs leading to the conclusion that TAVI may be cost-effective for this patient group.

Conclusion

The first major RCT, the PARTNER trial, showed that TAVI was not inferior to surgical AVR with regard to mortality in high-risk surgical patients. TAVI and surgery resulted in a similar improvement in quality of life. TAVI was however associated with an increase in major vascular complications and neurological adverse events, and with a higher rate of moderate to severe paravalvular regurgitation compared with AVR, which in turn was associated with increased late mortality.

The second major RCT, the CoreValve US trial, reported that TAVI was superior to surgical AVR with regard to mortality at 1 year and 2 years. Reported QoL was similar between the TAVI and AVR groups. TAVI was associated with an increased risk of vascular complications and permanent pacemaker insertion. AVR was associated with an increased risk of major bleeding events, neurovascular events (all stroke), acute kidney injury and new or worsening atrial fibrillation.

The PARTNER trial used only the SAPIEN™ valve and utilised only TF or TA implantation in operable patients. The CoreValve US trial used only the Medtronic CoreValve® System and included TF and TA access routes. There is no published RCT evidence comparing other TAVI devices or alternative implantation routes with surgical AVR.

TAVI technology continues to advance with substantial device modification in each new generation of TAVI devices. TAVI registry data provide broader evidence for TAVI outcomes in clinical practice, but the published data available for review does not fully capture the current stage of progress in the evolution of device modification and patient selection.

Another reason historical trial and registry data may also not reflect outcomes in current practice is that relatively inexperienced TAVI centres may be overrepresented in the data. This is due to studies being

done in the context of a period of expansion of TAVI services. Some evidence is available to suggest that TAVI procedural performance (Alli et al 2016) and outcomes (Lunardi et al 2016) improve as centres obtain more experience. Hospital length-of-stay following TAVI procedures has shown downward trend, below that reported in key trials, in the UK TAVI registry and in the Edinburgh TAVI service (personal communication). This will tend to improve TAVI cost-effectiveness.

A major weakness of the evidence base is the inconsistency in the definition of high surgical risk in published studies. In particular, there was a mismatch between the levels of surgical risk specified in the inclusion criteria of the pivotal studies and the observed mortality in the AVR groups reported in the results. This complicates the interpretation of the evidence base and formulation of advice for TAVI across specific subgroups. Patient selection criteria are often not consistently reported in registry-based analysis which hinders the use of this evidence in health technology assessment.

Data collated so far in the UK and other registries indicate better mortality outcomes among patients who are eligible for TF implantation. The UK data showed no difference in survival at any time point between SAPIEN and CoreValve devices, but did indicate higher incidence of clinically important paravalvular regurgitation and requirement for new pacemaker implantation with CoreValve compared with SAPIEN devices

A large body of evidence from observational studies of uncertain quality has been summarised in the secondary literature. TAVI outcomes from many clinically heterogeneous and mostly uncontrolled studies have been combined in large meta-analyses. These meta-analyses are of limited use for comparing TAVI with standard care in high risk patients or easily generalising pooled treatment effects to particular patient groups, TAVI devices or implantation routes.

There is currently limited information on the durability of implanted TAVI devices because studies published to date lack sufficient follow-up.

An adaption of the latest published economic evaluation to the Scottish context, utilising the CoreValve US trial data, indicated that TAVI may be a cost-effective option compared to AVR in this patient group. Cost-effectiveness is contingent upon TAVI device costs being less than £19,500-£24,000 and survival benefits from TAVI comparable to those observed in the CoreValve US trial. Published cost-effectiveness evidence prior to the CoreValve US trial tended to indicate that compared with AVR, TAVI is not a cost-effective treatment option for AS patients at high surgical risk. Two out of six previous economic evaluations demonstrated that TAVI may be cost effective, while the other four studies found TAVI may be either dominated by AVR or associated with a high cost per QALY.

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