

Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults who are not eligible for surgery

What is an evidence note

Evidence notes 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 and are produced in an approximately 3-month period. 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) produce an Advice Statement to accompany all evidence reviews.

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.

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 between 4 and 11 September 2013 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline in process, Embase, Cinahl and Web of Science databases were searched for systematic reviews and meta-analyses.

Key points

- Rapid progress is being made in transcatheter aortic valve implantation (TAVI) 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.
- In the randomised controlled PARTNER trial (cohort B), TAVI significantly reduced the risk of death from any cause after 1 year compared with medical management in patients who were unsuitable candidates for surgery. The reduction was sustained up to 2 years of follow up.
- In the PARTNER trial (cohort B), TAVI significantly improved quality of life up to 1 year of follow up compared with medical management in patients who were unsuitable candidates for surgery.
- In the PARTNER trial (cohort B), TAVI was associated with a significantly higher incidence of major vascular complications and neurological adverse events including stroke.
- There is conflicting evidence surrounding the cost effectiveness of TAVI compared with medical management in inoperable patients with severe aortic stenosis.
- Two out of three UK economic evaluations concluded that TAVI may be cost effective. In contrast, three out of five non-UK analyses suggested that TAVI may not be cost effective.
- A key driver within the economic evaluations for the inoperable patient group is the assumption relating to the respective mortality rates of TAVI and medical management. Where TAVI has been assumed to be associated with an absolute annual mortality reduction of $\geq 20\%$ compared with medical management, the economic evaluation tended to conclude that TAVI may be cost effective.

The primary literature was systematically searched between 4 and 11 September 2013 using the following databases: Medline, Medline in process, Embase, Cinahl and Web of Science. Results were limited to English language studies from 2011 to 2013.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials. Websites of organisations related to this topic were also searched, for example the United Kingdom (UK) TAVI registry, British Cardiovascular Society, European Society of Cardiovascular Surgery and American College of Cardiology.

Concepts used in all searches included: AS, TAVI, percutaneous aortic valve replacement (PAVR), and TAVI device brand names. A full list of resources searched and terms used are available on request.

Introduction

This evidence note, together with evidence note 52 (TAVI for severe symptomatic aortic stenosis in adults at high surgical risk), updates evidence note 38 published in August 2011¹. It summarises the clinical and cost-effectiveness evidence from published secondary sources, randomised controlled trials (RCTs) and economic evaluations comparing TAVI with medical management in adults with severe symptomatic AS who are not eligible for surgery. Additional data from the UK and other European TAVI registries are also included.

Epidemiology

AS is the most common native heart valve disease in adults in Europe². In most cases, the aetiology is degenerative, increasing with age due to degenerative calcification and therefore it is most often seen in the elderly^{2,3}. The key diagnostic tool for AS and its severity is echocardiography. 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^{4,5}. Without intervention, patients with severe symptomatic AS

have a poor prognosis with an average survival of 2–3 years⁵ and survival rates of only 15–50% at 5 years⁶. It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for surgical aortic valve replacement (AVR)^{3,7}. 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 is indicated in patients with severe symptomatic AS who, as assessed by a multidisciplinary 'heart team', are not suitable for AVR and are likely to gain improvement in their quality of life (QoL) and to have a life expectancy of more than 1 year after consideration of their comorbidities⁶. The current alternative for these patients is conservative palliative medical management with or without balloon aortic valvuloplasty (BAV)^{5,8}. TAVI is also used as an alternative to surgery for operable patients at high surgical risk⁷⁻⁹.

The population prevalence of patients likely to benefit sufficiently from TAVI has yet to be established^{7,9}. Analysis of currently available evidence from population-based studies in Europe and the US suggests that 12.3% of inoperable patients with severe symptomatic AS aged >75 years are potential candidates for TAVI⁴. Projections 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)⁴. This gave an estimated 2,217 (95% CI 896 to 3,904) new potential TAVI candidates each year⁴. This would equate to approximately 220 people (95% CI 90 to 390) 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 groin⁹⁻¹¹. 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 recently introduced 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 the Engager™ valve with a TA delivery catheter¹² in 2013. Five other TAVI devices currently have CE mark approval (Table 1), and several more are in various stages of development^{8,9,11,13}.

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)
Lotus™ Valve System (Boston Scientific Inc., Natick, Massachusetts)

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 UK¹⁴. Consensus governance recommendations require that centres providing a TAVI service contribute procedural, outcomes and follow-up data to the UK TAVI registry for every case^{7,14}. The UK TAVI registry recorded 1,029 TAVI cases in England and Wales between January 2007 and June 2011¹⁴. Published data for patients treated from January 2007 to December 2009 pertain to use of the SAPIEN and CoreValve devices approved for TF implantation in 2007 and TA implantation (SAPIEN) in 2008¹⁵. SAPIEN valve implantation was either TF or TA, and CoreValve TF, subclavian or occasionally direct aortic access.

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. TAVI is currently provided only for patients who, based on multidisciplinary team (MDT) assessment, are not suitable candidates for surgical AVR. All TAVI procedures are recorded in the National Institute for Cardiovascular Outcomes Research registry that uses a dataset produced by the British Cardiovascular Intervention Society (BCIS) and Society of Cardiothoracic Surgeons (SCTS).

Patient selection

Patient selection for TAVI is largely determined by clinical judgement on an individual patient basis and should, therefore, be undertaken by the MDT including interventional cardiologists, cardiac surgeons, a cardiac anaesthetist, and an expert in cardiac imaging^{7,16}.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons (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 the MDT^{8,17}.

Clinical effectiveness

Overview

Published results are available from one RCT comparing TAVI with medical management in inoperable patients¹⁸. The multicentre PARTNER trial, sponsored by Edwards Lifesciences, recruited patients at 22 sites in the US, three 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 BAV) (cohort B). Results for cohort B at 1-year¹⁸ and 2-year¹⁹ follow up have been published. Results after 3-years' follow up have been released by the manufacturer but are not yet published¹³ (Edwards Lifesciences news release, 24 October 2012).

On completion of recruitment to cohort B in the PARTNER trial, further inoperable patients were recruited to a randomised continued access study until recruitment to cohort A in the pivotal trial was completed^{20,21}. Once recruitment to cohort A was completed, randomisation in the continued access study was discontinued and enrolment was expanded to include high-risk operable patients. Some results from the randomised continued access study of inoperable patients were presented at the US Food and Drug Administration (FDA) panel meeting on TAVI^{22,23} but the data are not published in full^{20,21}. The non-randomised continued access study is ongoing²⁴.

Although the PARTNER trial appears to have been generally well conducted, it is unclear from the reported randomisation methods that adequate steps were taken to avoid selection bias. There were some differences in potential prognostic variables at baseline between TAVI and control group patients. The generalisability of the trial's findings is limited by the exclusion of important patient subgroups including patients with severe peripheral vascular disease and patients requiring treatment of coronary stenosis¹⁸. The use of BAV in 83.8% of patients in the medical management control group is not routine practice in Scotland

but clinical experts consider that it does not limit the generalisability of the trial results to patients in Scotland (National Planning Forum TAVI Subgroup. Personal communication, 15 Nov 2013). No ongoing RCTs comparing TAVI with medical management in inoperable patients were identified. Medtronic received approval from the FDA to evaluate TAVI in inoperable patients using a non-randomised study design in the US CoreValve Pivotal Trial²⁵, with a composite primary endpoint of all-cause mortality or major stroke at 12 months comparing TAVI with an Objective Performance Goal (OPG) based on the PARTNER trial Cohort B control group outcomes and a meta-analysis of BAV case series. Published data were not available for inclusion at the time of writing this evidence note (results for patients who underwent TF TAVI have been published since²⁵).

The National Institute for Health and Care Excellence (NICE) updated its interventional procedure (IP) guidance on TAVI for AS in March 2012¹⁶ based on a rapid review of literature published to 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 reports²⁶. Several technology assessments dating from publication of the PARTNER trial results have assessed the clinical effectiveness of TAVI in inoperable patients. Some based their assessment solely on the PARTNER trial^{20,27} while others also considered evidence from observational studies^{13,28-30}. Two health technology assessments (HTAs) focused on outcomes beyond 1 year^{28,29}.

A systematic review that pooled data from observational studies comparing TAVI with medical management without taking account of the potential for confounding was not included in this evidence note³¹. Several meta-analyses reporting pooled estimates for TAVI outcomes without a comparator³²⁻³⁸ were also excluded. Although the total numbers of patients in these meta-analyses are impressive, they combined clinically heterogeneous studies of unknown quality. There was variation in the baseline risk in the populations studied, the TAVI devices and routes of implantation, and, consequently, event rates varied widely between studies. The utility of these publications is, therefore, limited. A systematic review that reported a narrative

summary of results from uncontrolled TA TAVI series was also excluded³⁹.

The UK TAVI registry has published outcomes with up to 2-year follow up for patients treated from January 2007 to December 2009¹⁵ and data comparing outcomes according to valve type and access route based on patients treated to December 2010⁴⁰. The European SOURCE registry funded by Edwards Lifesciences has published 1-year outcomes for patients treated from November 2007 to January 2009⁴¹. The SOURCE and Italian registries have published data on survival at 2^{42,43} and 3⁴³ years following TA implantation. An independent multinational European registry, including UK TAVI registry data, has published in-hospital outcomes for patients treated from January 2011 to June 2012⁴⁴. The publications report demographic data, including the average STS and/or logistic EuroSCORE, and outcomes for patients grouped by TAVI implantation route but do not categorise patients by surgical status as inoperable or high risk.

TAVI versus medical management

PARTNER trial cohort B

The eligibility criteria for cohort B in the PARTNER trial included agreement among a cardiologist and at least two cardiovascular surgeons that coexisting conditions precluded surgery on the basis of a predicted $\geq 50\%$ probability of surgical mortality at 30 days or serious irreversible morbidity¹⁸. Patients found to have severe peripheral vascular disease that precluded TF access were excluded. The main primary outcome was all-cause mortality at 1 year (Kaplan-Meier analysis). Analysis was by intention-to-treat for effectiveness outcomes and 'as treated' for adverse events¹⁸. After completion of 1-year follow up, patients in the control group could cross over to the TAVI group, and data from those patients were censored at cross over¹⁹.

Of the 358 patients recruited to cohort B, 179 were allocated to TF TAVI and 179 to medical management, of whom 150 (83.8%) underwent BAV (114 within 30 days of randomisation and 36 >30 days after randomisation)¹⁸. The mean age of patients in both groups was 83 years (standard deviation (SD) 8.6 TAVI group, 8.3 control group). The mean baseline logistic EuroSCORE was lower in the TAVI group (26.4, SD 17.2) than in the control group (30.4, SD 19.1) whereas the

mean STS scores were similar (11.2, SD 5.8 and 12.1, SD 6.1, respectively). Compared with the TAVI group, more patients in the control group had atrial fibrillation (48.8% versus 32.9%), chronic obstructive pulmonary disorder (52.5% versus 41.3%), frailty (28.0% versus 18.1%), prior BAV (24.4% versus 16.2%), prior coronary artery bypass graft (45.6% versus 37.4%), and prior myocardial infarction (MI) (26.4% versus 18.6%), whereas more patients in the TAVI group had porcelain aorta (19.0% versus 11.2%) and prior percutaneous coronary intervention (PCI) (30.5% versus 24.8%)¹⁹.

Despite their inoperable status, 21 patients in the control group underwent surgical intervention including AVR (12 patients), left ventricular apical-aortic conduit and AVR (five patients), and TAVI (four patients). In the TAVI group, TF access was unsuccessful in two patients and two procedures were aborted because of inaccurate intraprocedural aortic annulus measurement¹⁸.

All-cause mortality at 1 year (median duration of follow up 1.6 years, range 1.0 to 2.8) was significantly lower in the TAVI group (30.7%) compared with the control group (50.7%) (hazard ratio (HR)=0.55; 95% CI 0.40 to 0.74; $p < 0.001$)¹⁸. The number needed to treat to prevent one additional death in the first year was five (95% CI 4 to 9) (estimated by Healthcare Improvement Scotland).

At 2 years, the rate of all-cause mortality was 43.3% in the TAVI group and 68.0% in the control group (HR=0.56; 95% CI 0.43 to 0.73; $p < 0.001$)¹⁹. Regression analysis indicated decreasing mortality benefit with TAVI with increasing STS score¹⁹. Unpublished results released by the manufacturer indicated 54.1% all-cause mortality at 3-years' follow up in the TAVI group and 80.9% in the control group¹³ (Edwards Lifesciences news release, 24 October 2012).

The mean length of hospital stay for TAVI patients was 10.1 days (SD 10.1 days; median 7 days) comprising a mean intensive care unit (ICU) stay of 4 days (SD 7 days; median 2 days) and mean non-ICU stay of 6.1 days (SD 5.4 days; median 5 days)⁴⁵.

Repeat hospitalisation due to AS or complications of the valve procedure was significantly lower in the TAVI group at 1 year (22.3% versus 44.1%; $p < 0.001$)¹⁸, as was repeat hospitalisation for

cardiac reasons at 2 years (35.0% versus 72.5%; $p < 0.001$)¹⁹.

A significantly higher proportion of survivors in the TAVI group compared with the control group were asymptomatic or had mild symptoms defined as NYHA functional class I or II at 1 year (74.8% versus 42.0%; $p < 0.001$)¹⁸ and 2 years (83.1% versus 42.5%; $p < 0.001$)¹⁹. Six-minute walk test distances at 1 year showed statistically significant improvement from baseline among TAVI patients who were able to undertake the test, and no significant change in the control group¹⁸.

Analysis of QoL showed a statistically significant difference in the primary outcome, mean Kansas City Cardiomyopathy Questionnaire (KCCQ) summary scores in favour of TAVI at 1, 6 and 12-month follow up⁴⁶. The mean difference at 12 months was 26 points (95% CI 18.7 to 33.3; $p < 0.001$). Based on heart failure outpatients, changes of around 5, 10 and 20 points correspond to physician-rated small, moderate and large clinical improvements. Results for the KCCQ subscales (symptoms, physical limitation, social limitation, self-efficacy, QoL) and the Short Form (SF)-12 Health Survey were similar⁴⁶.

Randomised continued access study

An additional 90 patients were enrolled in the randomised cohort B continued access study, which showed a lower mortality rate in the medical management group at 1 year compared with TAVI. These are conflicting results when compared with the pivotal trial^{20,22}. One-year mortality was 34.3% with TAVI and 21.6% with medical management, a 12.7% increase in absolute risk, compared with the 20% reduction in absolute risk shown in the pivotal trial (30.7% with TAVI and 50.7% with medical management)^{20,22}. The continued access study was not powered to demonstrate non-inferiority or benefit, and between-group analysis was not conducted due to the small sample size²².

Data shown in the FDA panel briefing document illustrated that on average patients in both groups walked a longer distance during a 6-minute walk test compared with baseline at 3 months, 6 months and 1 year²².

Secondary evidence

NICE concluded that the evidence on the efficacy of TAVI was adequate for patients who

are unsuitable for surgical AVR, and TAVI may, therefore, be used with normal arrangements for clinical governance, consent and audit¹⁶. The PARTNER trial cohort B was the only comparative study reviewed²⁶.

The results from the PARTNER trial cohort B have been reported in several technology assessments reiterating that TAVI improved survival and QoL compared with standard care for patients ineligible for surgery^{13,27-30}. These sources included little or no evidence on clinical-effectiveness outcomes from studies other than the PARTNER trial.

In addition to the published 1-year outcomes from the PARTNER trial, the Belgian HTA presented results of a subgroup analysis provided by the study sponsor illustrating 24.5% mortality at 1 year in TAVI patients who were inoperable for anatomical reasons (thoracic wall malformation, repeated previous thoracic surgeries, porcelain aorta, sequelae of radiotherapy) and 33.3% in patients who were inoperable for medical reasons (comorbidities)²⁰. Comparing TAVI with medical management, this represented a reduction of 27.9% in anatomically inoperable patients and 17% in medically inoperable patients²⁰.

Only the Belgian HTA included results from the PARTNER trial cohort B randomised continued access study, noting that it did not confirm the favourable effect of TAVI on all-cause mortality at 1 year shown in the pivotal trial²⁰. Data from the continued access study were not available to enable subgroup analysis of anatomically inoperable and medically inoperable patients²⁰.

TAVI registry data

The UK TAVI registry reported a 97.2% (846/870) procedural success rate using Edwards SAPIEN and CoreValve devices implanted by TF and other routes between 2007 and 2009 at 25 accredited centres in England and Wales¹⁵. 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) implantation⁴⁰.

The UK TAVI registry (2007–2009) reported 78.6% survival at 1 year and 73.7% at 2 years overall (Kaplan-Meier analysis); and a statistically significant difference in mortality between TF and non-TF patients at 1 year (18.5% versus 22.7%;

$p=0.002$) and 2 years (22.5% versus 36.7%; $p<0.001$)¹⁵. The SOURCE registry (2007–2009) reported 76.1% survival at 1 year; 81.1% for TF and 72.1% for TA⁴¹. Two-year survival following TA TAVI was similar to the UK in the SOURCE registry (65.1%)⁴², but higher in the Italian TA TAVI registry (2008–2012) that recorded 76.1% (SD 1.9) survival at 2 years and 67.6% (SD 3.2) at 3 years⁴³.

The UK TAVI registry has not reported on length of stay in hospital. An independent prospective registry of consecutive patients who underwent TAVI between 2011 and 2012 in 137 centres in 10 European countries reported wide variation in the duration of hospital stay from 5 to >12 days (mean 9.3 days, SD 8.1 days)⁴⁴. The FRANCE 2 registry of patients treated between January 2010 and October 2011 recorded a mean length of hospital stay of 11.1 days (SD 8.0) and mean ICU stay of 4.9 days (SD 4.8)⁴⁷. The mean length of hospital stay was 10.5 days (SD 8.1) for TF patients, 13.3 days (SD 7.8) for TA patients, and 11.6 days (SD 6.0) for subclavian implantation patients; 10.9 days (SD 7.5) for SAPIEN device recipients and 11.3 days (SD 8.9) for CoreValve recipients⁴⁷. The Italian registry has reported a mean hospital stay of 9 days (SD 4 days) and median ICU stay of 2 days (quartiles 1 to 3) following TA implantation in patients treated between April 2008 and September 2010⁴⁸. A SOURCE registry analysis compared patients who received TA TAVI between January 2008 and January 2009 with those implanted between February 2009 and December 2009 and showed a reduction in the median ICU length of stay from 2 days (range 0 to 89 days) to 1 day (range 0 to 53 days) ($p=0.03$)⁴⁹.

Safety

PARTNER trial cohort B

During or within 24 hours of the TAVI procedure, valve embolisation occurred in one patient (0.6%), and two patients underwent multiple (≥ 2) valve implantations¹⁸.

The trial found no statistically significant difference in 30-day mortality between TF TAVI (5.0%) and medical management including BAV (2.8%) ($p=0.41$)¹⁸.

Major vascular complications were significantly more common in the TAVI group at 30 days (16.2% versus 1.1%; $p<0.001$) and 1 year (16.8%

versus 2.2%; $p<0.001$)¹⁸. The rate of major stroke was 5.0% in the TAVI group versus 1.1% in the control group at 30 days ($p=0.06$) and 7.8% versus 3.9% at 1 year ($p=0.18$)¹⁸. The overall rate of stroke was significantly higher in the TAVI group at 1 year (11.2% versus 5.5%; $p=0.001$) and 2 years (13.8% versus 5.5%; $p=0.001$)¹⁹. The excess of strokes in the TAVI group beyond 30 days and up to 2 years was attributable to a higher rate of haemorrhagic strokes¹⁹.

Major bleeding events were significantly more common in the TAVI group at 30 days (16.8% versus 3.9%; $p<0.001$)¹⁸ and 1 year (24.2% versus 14.9%; $p=0.04$)¹⁹, but not significantly different at 2 years (28.9% versus 20.1%; $p=0.09$)¹⁹.

Moderate or severe paravalvular aortic regurgitation was present in 11.8% of TAVI patients at 30 days and in 10.5% at 1 year¹⁸. Three patients (1.7%) underwent a repeat TAVI procedure to treat clinically significant aortic regurgitation (2 paravalvular, 1 transvalvular)¹⁸. Kaplan-Meier analysis of TAVI patients stratified according to 'moderate to severe' and 'none to mild' post-procedural paravalvular aortic regurgitation indicated no statistically significant difference in cardiac mortality or all-cause mortality (moderate to severe 35.3%, none to mild 27.2%) at 1 year (p values not reported) or at 2 years (cardiac mortality 36.7% versus 27%, $p=0.38$; all-cause mortality 41.2% versus 40.5% $p=0.89$)¹⁹.

There was no statistically significant difference in the number of patients requiring a new pacemaker at 30 days (3.4% in the TAVI group, 5% in the control group), 1 year (4.7% TAVI, 8.6% control) or up to 2 years (6.4% TAVI, 8.6% control)^{18,19}. There was also no statistically significant difference in rates of MI, acute kidney injury or renal failure^{18,19}.

Randomised continued access study

In the randomised continued access study, all-cause mortality at 30 days was 9.8% in the TAVI group and 2.1% in the control group^{20,22}. Data reported in the FDA panel briefing document showed 97.5% freedom from major stroke following TAVI and 100% in the control group at both 30 days and 1 year²². These mortality results were obtained from Kaplan-Meier analysis of intention-to-treat data. The FDA document also reported that the most common site-reported

severe adverse events in the as-treated population were heart failure (15% of patients in the TAVI group, 24.5% in the control group), infection including endocarditis (17.5% TAVI, 6.1% control) and respiratory event (20% TAVI, 4.1% control)²².

Secondary evidence

NICE IP guidance states that evidence on the safety of TAVI shows the potential for serious but well-recognised complications¹⁶. It recommends that units undertaking TAVI should have cardiac and vascular surgical support for emergency treatment of complications¹⁶. NICE recommended that further research should include outcomes such as the incidence of stroke and other adverse events, aortic regurgitation and valve durability as well as symptom relief and QoL¹⁶.

HTAs confirm the evidence of increased risk of serious adverse events associated with TAVI, including major vascular complications and neurological events^{13,20,27-30,50}.

The available secondary evidence indicates that few studies have published data on the durability of implanted TAVI devices beyond 1 year^{26,28-30}. In one Canadian report of 5-years' follow up⁵¹, signs of moderate prosthetic valve failure were observed in 3/88 (3.4%) patients who underwent TAVI with the Edwards SAPIEN or a previous generation Cribier device²⁹. There were no cases of structural deterioration of Edwards SAPIEN valves in another Canadian patient series (n=70)⁵² with a median follow up of 3.7 years (interquartile range (IQR) 3.4 to 4.3) at which point the survival rate was 57% (n=40)^{26,30}. Four-year follow-up assessment of 20 patients who received CoreValve implants in a multicentre study in Europe and Canada⁵³ found no frame fractures, valve migrations or valve endocarditis, and no structural valve deteriorations leading to stenosis or regurgitation²⁸.

TAVI registry data

The UK TAVI registry (2007–2009) reported 7.1% mortality at 30 days; this was lower among TF patients (n=599) compared with non-TF (n=271) patients (5.5% versus 10.7%; $p=0.006$)¹⁵. The TF patients had a lower median logistic EuroSCORE (17.1, IQR 11.1 to 25.5) compared with non-TF patients (21.4, IQR 14.4 to 33.6). Data for patients treated to December 2010 showed 4.4%

mortality at 30 days following TF implantation using the SAPIEN valve (n=387) and 5.1% for CoreValve (n=704), and 11.2% following TA implantation (SAPIEN, n=408) and 3.2% for subclavian (CoreValve, n=94)⁴⁰. The SOURCE registry (2007–2009) reported 30-day mortality of 6.3% for TF implantation (n=463) and 10.3% for TA (n=575) using the SAPIEN valve⁵⁴. The larger FRANCE 2 register of patients treated in 2010–2011 reported higher rates for TF (8.5%, n=2361), TA (13.9%, n=567) and subclavian (10.1%, n=184) implantation⁴⁷.

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% versus 1.9%; $p<0.001$)¹⁵. In the SOURCE registry (2007–2009), rates of major access and non-access vascular complications were TF 10.6% and TA 2.4%⁵⁴.

Using standardised Valve Academic Research Consortium (VARC) definitions, the FRANCE 2 registry (2010–2011) reported major bleeding rates of 1.5% TF, 3.4% TA and 3.3% subclavian ($p<0.001$) but found no statistically significant difference in life-threatening bleeding among the three approaches⁴⁷.

The incidence of procedure-related stroke (≤ 30 days) was 4.1% in the UK TAVI registry (2007–2009), with no statistically significant difference between TF and other routes, or between SAPIEN and CoreValve devices¹⁵. The UK registry (2007–2010) showed in-hospital stroke rates of 3.3% (SAPIEN) and 3.0% (CoreValve) following TF implantation, and 3.4% TA (SAPIEN) and 2.1% subclavian (CoreValve)⁴⁰. The incidence of procedure-related stroke (≤ 30 days) was 2.5% in the SOURCE registry (2.4% TF, 2.6% TA)⁵⁴, and similar (3–5%) in several independent European registry reports^{47,48,55}.

The FRANCE 2 registry reported a 4.1% incidence of stroke and 2.3% major stroke at 1 year overall, the latter being similar for TF, TA and subclavian implantation⁴⁷. The SOURCE registry showed 95.5% freedom from stroke at 1 year overall⁴¹ using Kaplan-Meier analysis, and 93.9% at 2 years following TA implantation⁴².

Post-procedural (≤ 30 days) moderate to severe (grade >2) paravalvular regurgitation was reported in 13.6% of patients in the UK TAVI registry (2007–2009), and was significantly more

common in the TF group compared with other routes (15.6% versus 9.1%; $p=0.01$) and with CoreValve compared with SAPIEN devices (17.3% versus 9.6%; $p=0.001$)¹⁵. Similar rates at 30 days were observed in the FRANCE 2 registry (2010–2011)⁴⁷. 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 CoreValve⁴⁰.

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 (2007–2009) ($p<0.001$)¹⁵; this was similar to the SOURCE registry (2007–2009) rate of 7.0% following SAPIEN valve implantation⁵⁴. At 1 year, the UK TAVI registry (2007–2010) showed that 6.7% (SAPIEN) and 22.6% (CoreValve) of TF patients required new permanent pacemaker implantation ($p<0.001$), as did 7.4% of TA (SAPIEN) implantation patients and 26.6% of subclavian (CoreValve) implantation patients (overall, 7.2% SAPIEN versus 23.1% CoreValve, $p<0.01$)⁴⁰. The FRANCE 2 registry (2010–2011) reported similar rates at 1 year, except that the rate of new pacemaker implantation following TA TAVI was around double that observed in the UK registry (2007–2010) (13.6% versus 7.4%)⁴⁷. The SOURCE (SAPIEN) registry showed 91.5% freedom from pacemaker implantation overall at 1 year⁴¹ using Kaplan-Meier analysis, and 91.1% at 2 years following TA implantation⁴².

The VARC has defined a composite safety endpoint at 30 days (including mortality, major stroke, serious bleeding, acute kidney injury, MI, major vascular complication, and repeat procedure for valve-related dysfunction) and at 1 year (including 30-day mortality, failure of current therapy for AS, and valve dysfunction)⁵⁶. In the Italian TA registry (2008–2012) 19.1% of patients met the VARC 30-day endpoint (21.7% by updated VARC-2 definitions)⁴³.

The long-term durability of bioprosthetic percutaneous 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^{9,11,57}. Published registry data lack sufficient follow up to provide useful information on the longer term durability of TAVI devices.

The Italian registry of TA implantation ($n=774$) observed no cases of structural deterioration of SAPIEN valves up to 3 years of follow up (median 12 months, range 1–44)⁴³.

Cost effectiveness

Three UK economic evaluations⁵⁸⁻⁶⁰ were identified in which TAVI was compared with medical management in patients with severe AS who are ineligible for conventional AVR. A fourth European economic evaluation was carried out from a Belgian perspective⁶¹. These four studies are considered most relevant to NHSScotland, and are described in detail below. It should be noted that medical management may include a BAV procedure for a number of patients, and this combination of treatments is often referred to as standard care.

A further four economic evaluations^{45,62-64} were identified, yet these studies were carried out from a North American perspective. Although their generalisability to NHSScotland is limited, the North American studies have been summarised since they were still considered to be useful to inform decisionmaking.

UK and Europe

In the first of these economic evaluations, Watt *et al.* (2012)⁵⁸ used a Markov model, which incorporated a 10-year time horizon and was developed from a UK NHS perspective.

The clinical effectiveness evidence used in the economic model was primarily drawn from the 1-year results of cohort B within the pivotal PARTNER trial. The key input to the model was the relative mortality rate of each arm, with the observed values in PARTNER cohort B extrapolated in order to generate lifetime costs and benefit estimates. As such, the assumption that TAVI was associated with a 20% reduction in mortality after 1 year was used in the economic model. It is also worth noting that, in the medical management arm, 83% of patients were assumed to receive a BAV procedure.

The results of the base-case analysis showed that in comparison to medical management, TAVI was associated with an increase in cost of £25,200 and a quality-adjusted life year (QALY) gain of 1.56. This resulted in a cost per QALY of £16,200.

An uncertainty surrounding the economic model stems from potential weaknesses relating to the PARTNER trial, for example the selective interpretation of the study results (for example no acknowledgment of the randomised continued access study)^{20,21,30,50,65,66}. Regarding uncertainties surrounding Watt *et al.*'s⁵⁸ model, there is a general lack of transparency. For example, it is not clear how the utility values are calculated for each health state, and furthermore the value for each state is not presented. This makes it difficult to assess the plausibility of the model inputs, leading to increased uncertainty surrounding the model outputs.

Since publishing their economic evaluation, Watt *et al.* responded to concerns raised surrounding the above uncertainties⁶⁵. In relation to questions surrounding internal validity, Watt *et al.*⁶⁵ noted that the PARTNER trial was an RCT and unquestioningly accepted that the imbalances in baseline characteristics occurred by chance. Regarding their QoL data, Watt *et al.*⁶⁵ replaced their original utility values with EQ-5D data from the PARTNER trial, which increased the cost per QALY to £20,100. Furthermore, Watt *et al.* had included a utility benefit in the TAVI arm of their economic model. Removing this benefit, so that an equal utility value was assumed for each health state regardless of whether the patient had received TAVI or medical management, increased the cost per QALY to £25,600.

The results of the initial economic evaluation suggest that TAVI is cost effective compared with medical management for inoperable patients. However, it must be noted that reasonable adjustments to some of the input parameters increases the cost per QALY from £16,200 to £25,600.

Within Murphy *et al.*'s (2013)⁵⁹ UK economic evaluation, two cost-utility analyses were presented. The first analysis is a de novo cost-effectiveness model that was populated by both the PARTNER trial cohort B results and by the authors' assumptions. The second analysis is a re-run of the first model but which incorporates more recent data regarding the longer term benefits for TAVI patients. Both analyses used a lifetime time horizon (assumed to be approximately 10 years), and are from a UK NHS perspective.

Utility estimates were drawn from the literature, while cost data included both the intervention costs, and the resource costs of the associated healthcare.

TAVI was found to be more effective than medical management with an incremental QALY gain of 0.44, and more costly with an incremental cost of £15,885. This led to an overall cost per QALY of £35,956. Based on a cost-effectiveness threshold of £30,000 per QALY, the probability that TAVI is cost effective was estimated to be 18%. This analysis revealed that for patients ineligible for surgery, TAVI is not cost effective compared with medical management.

In the second analysis, TAVI remained more costly, but was now assumed to be much more effective, with an incremental QALY gain of 1.58. This resulted in an overall cost per QALY of £19,064. As such, TAVI was now said to be cost effective.

Much of the variation between the two analyses appears to stem from the percentage reduction in all-cause mortality associated with TAVI at the end of year 1. In the first analysis, this figure was 14%, which was increased to 31% in the second analysis. Based on the references presented in the report, this appears to be an optimistic improvement. The only TAVI study upon which the changes are based does not contain a comparator arm, and therefore there is little evidence to support the assumption that compared with medical management, the percentage reduction in all-cause mortality associated with TAVI is improved two-fold.

In the third UK economic evaluation, the key outcomes within Orlando *et al.*'s study – overall survival and hospitalisation-free survival – were based on the results of the PARTNER trial cohort B⁶⁰. As such, the model extrapolated longer term survival based on the assumption that TAVI leads to a 20% reduction in mortality after year 1. The Markov model was based on a 25-year time horizon and built from an NHS perspective.

The results of the base-case analysis showed that TAVI was associated with an incremental cost of £24,147 and an incremental QALY gain of 1.87. This resulted in an overall cost per QALY of £12,900, which indicates that TAVI is cost effective compared with medical management in patients unsuitable for surgery.

There are various limitations with the study. The first of these surrounds the model structure, whereby the authors suggest that for future work, additional data should be included based on an agreed model structure. Orlando *et al.*'s current model structure was restricted to only two health states, which represents a very simplified depiction of clinical practice. Orlando *et al.* go on to mention other limitations within their analysis. In particular, the authors comment that the extent to which PARTNER data can be applied is debatable, and the authors also note the seriously unstable utility values used in their analysis.

In Belgium, a cost-utility analysis was carried out by Neyt *et al.* (2012)⁶¹ for patients with severe AS to compare TAVI with non-surgical standard care (including BAV) in inoperable patients. A Markov model was used, where a lifetime time horizon was applied.

The model was created from a Belgian perspective which means the generalisability of the model results to NHSScotland is limited relative to the UK studies. The clinical-effectiveness data used in the economic model were drawn from the results of the pivotal PARTNER trial cohort B. The key outcome was mortality rate, with the observed values in the trial extrapolated in order to generate lifetime costs and benefit estimates.

The authors' base-case analysis incorporates the results of the unpublished (but publicly available) continued access study where, following the same protocol, an increase in mortality after 1 year was found for the TAVI arm compared with the medical management arm. Combining the results of the continued access study with the original PARTNER cohort B findings, results in a weighted average mortality reduction associated with TAVI of 12.3% after year 1.

QoL was modelled using EQ-5D data collected during the PARTNER trial, with utility measured at baseline, 1 month, 6 months, and 12 months. These values are not published but were supplied to the authors by the PARTNER trial sponsors. Costs included the intervention costs, and costs associated with health service resource use such as hospitalisations and adverse events.

The results of the base-case analysis showed that in comparison to standard care, TAVI was associated with an increase in cost of €33,200 (£27,755) and a QALY gain of 0.74. This resulted

in a cost per QALY of €44,932 (£37,564). Various sensitivity analyses were carried out, with the following variables all found to increase the incremental cost per QALY; a reduction in time horizon and the application of recommended UK discount rates. The authors also differentiated between non-anatomically inoperable and anatomically inoperable patients, and commented that the cost per QALY estimate may be around €11,000 (£9,168) lower for the latter group and around €5,000 (£4,167) higher for the former group.

In terms of weaknesses associated with the analysis, the study is undertaken from a Belgian perspective, which reduces the generalisability of the cost data to the UK. The cost data are also drawn from relatively few, early experiences of TAVI and therefore may not be reflective of current practice. Furthermore, the model incorporates data from the continued access study to which there are few published references.

North America

Four cost-utility analyses from North America (two from the US^{45,62} and two from Canada^{63,64}) were identified which assessed the cost effectiveness of TAVI compared with standard care in inoperable patients with severe AS. The key features and results of these studies are described briefly below, although these are of limited generalisability to the UK due to the variation in healthcare systems and the application of a different discount rate to those used in UK studies.

The first US study is a cost-utility analysis undertaken to assess the relative costs and benefits of TAVI compared with standard care in patients with severe AS that are ineligible for conventional AVR⁴⁵. The economic model was created from a US perspective and based on a lifetime time horizon. The clinical-effectiveness data used to populate the economic model are directly based on the results of the PARTNER trial cohort B, where TAVI is associated with a 20% improvement in 1-year mortality compared with standard care.

The results of the study found that TAVI generated an additional 1.3 QALYs, and at an increased cost of \$79,837 (£48,545). As such, the incremental cost effectiveness of TAVI was estimated to be \$61,889 (£37,632) per QALY.

Reynolds *et al.* conclude that TAVI is cost effective, although their result is above commonly accepted UK cost-effectiveness thresholds. The results of the economic model are sensitive to the modelling approach. If alternative – and plausible – survival functions are applied to the TAVI arm, the cost per QALY increases towards \$70,000 (£42,564).

Simons *et al.* (2012)⁶² also set out to assess the cost effectiveness of TAVI in inoperable patients with severe AS. The comparator in the Markov model was medical management, where a lifetime time horizon (assumed to be 25 years) was used. The relative mortality rate between TAVI and standard care was estimated based on both the PARTNER trial cohort B data and a systematic review comparing overall survival rates between TAVI and standard care. The systematic review estimated that the difference in 1-year mortality rate between TAVI and standard care is 13%.

The model estimated that TAVI would increase quality-adjusted life expectancy by 0.70 QALYs, and increase lifetime costs by \$85,600 (£52,049), which led to an overall cost per QALY of \$116,500 (£70,838). This figure is substantially larger than the result of the Reynolds *et al.* study⁴⁵, which Simons *et al.* attribute to their use of different methods of estimating longer term survival. Simons *et al.* go on to argue that their methods are consistent with longer-term outcomes in several registry studies – although the general low-quality nature of registry study evidence means the evidence to support their mortality rate assumption may not be robust.

The Canadian economic evaluations were also designed to assess the cost effectiveness of TAVI compared with medical management in inoperable patients with severe AS. The studies used a discount rate of 5%, which is greater than the recommended UK rate.

The first of these studies – carried out by Hancock-Howard *et al.* (2013)⁶³ – used a decision analytical model over a 3-year time horizon, which was populated primarily based on the results of the PARTNER trial cohort B for key inputs such as estimated survival, QoL, and resource utilisation. The survival improvements associated with TAVI were assumed to be 20% after 1 year and 25% after 2 years.

Over the time horizon, TAVI was associated with an incremental QALY gain of 0.49 and an incremental cost of \$15,687 (£8,504), resulting in a cost per QALY of \$32,170 (£17,440). As such, the authors concluded that TAVI is cost effective relative to medical management.

The second Canadian study, by Doble *et al.* (2013)⁶⁴, used a Markov model over a 20-year time horizon to assess the cost effectiveness of TAVI. Consistent with many previous studies, the model was populated using the data from the PARTNER trial cohort B, which included the assumption that TAVI leads to a 20% reduced mortality risk after 1 year.

The results of the model demonstrated that TAVI was associated with an incremental QALY gain of 0.60 and an incremental cost of \$31,028 (£16,821). This led to an overall cost per QALY of \$51,324 (£27,823). Based on a US willingness-to-pay threshold of \$49,000 (£26,563) per QALY, there was found to be a 44% chance that TAVI was cost effective and thus a 56% chance that standard care is the cost-effective option. However, the authors' TAVI cost assumptions have been argued to be an overestimate of Canadian TAVI costs⁶⁷.

Sehatzadeh *et al.* (2013)²⁷ carried out a cost-utility analysis – comparing TAVI with standard care – on behalf of Health Quality Ontario (HQO). This analysis appears to be an updated analysis of the Doble *et al.* study described above, and follows on from the criticisms of the TAVI cost data⁶⁷. Using updated cost data supplied by the manufacturer (Edwards Lifesciences Canada), the cost per QALY fell to \$24,257 (£13,150). It must be noted that the updated analysis also included additional QoL gains for the TAVI arm after 1 year.

Summary of cost effectiveness

Based on the economic evaluations included in this report, there is conflicting evidence surrounding the cost effectiveness of TAVI compared with medical management for AS patients who are ineligible for surgery. Two of the three UK studies concluded that TAVI may be cost effective^{58,60} in addition to two out of four North American analyses also confirming that it may be a cost-effective option^{63,64}, while a Belgian study suggested that TAVI may not be cost effective⁶¹.

In attempting to decipher the results of the economic evaluations, it is perhaps worth drawing attention to the negative correlation between percentage reduction in mortality and the overall cost per QALY. This may seem an obvious correlation, but the pattern across the numerous studies presented here provides reassurance surrounding the important impact that relative mortality assumptions have on the overall cost-effectiveness conclusions. The PARTNER trial used to inform each one of the economic evaluations provides useful evidence regarding the relative impact that TAVI has on mortality. Where the economic evaluations have directly drawn on the PARTNER cohort B data – that is assuming TAVI to be associated with a 20% improvement in mortality relative to medical management after 1 year – the economic evaluations have tended to conclude that TAVI is cost effective. To help illustrate this, a summary has been presented in Table 2 which shows, for each study, the assumed TAVI mortality reduction and the base-case incremental cost-effectiveness ratio (ICER). Table 2 also includes the TAVI device cost used within each evaluation, although some of the studies only presented the overall procedure costs.

It should be noted that there are of course a number of other inputs upon which the economic evaluations are based. However, limited transparency within the literature meant that it was difficult to compare variations in these inputs across the economic evaluations, and subsequently it is difficult to detect how patterns in these other inputs tended to affect the economic conclusions.

There are also various uncertainties and weaknesses to consider alongside the economic evaluations. For example, and owing to the fact that each of the economic evaluations uses PARTNER data to populate the model, attention must be drawn to the potential limitations of the PARTNER trial^{20,21,30,50,65,66}.

In summary, although there is evidence to support the cost effectiveness of TAVI for patients with severe AS who are ineligible for surgery, the findings must be treated with caution for two reasons; firstly, some analyses found that TAVI may not be cost effective and, secondly, there are some uncertainties surrounding the model inputs used in the economic evaluations.

Table 2 Cost-effectiveness summary data

Study	TAVI mortality reduction	TAVI device cost	Base case ICER
Watt <i>et al.</i> , 2012	20%	£524.40 (procedure cost per hour)	£16,200
Murphy <i>et al.</i> , 2013	a) 14% b) 31%	£12,000	a) £35,956 b) £19,064
Orlando <i>et al.</i> , 2013	20%	£24,000 (procedure cost)	£12,900
Neyt <i>et al.</i> , 2012	12.3%	€43,571 (£36,352)	€44,932 (£37,564)
Reynolds <i>et al.</i> , 2012	20%	\$30,000 (£18,160)	\$61,889 (£37,632)* *authors concluded cost effective
Simons <i>et al.</i> , 2012	13%	\$63,054 (£38,168) (procedure cost)	\$116,500 (£70,838)
Hancock-Howard <i>et al.</i> , 2013	20% (25% after 2 years)	\$24,408 (£13,215)	\$32,170 (£17,440)
Doble <i>et al.</i> , 2013.	20%	\$37,606 (£20,361)	\$51,324 (£27,823)
Sehatzadeh <i>et al.</i> , 2013		\$24,000 (£12,994)	\$24,257 (£13,150)

Conclusion

The only RCT, the PARTNER trial, showed that TF TAVI significantly reduced mortality for up to 2 years of follow up compared with medical management in inoperable patients, and QoL assessed up to 1 year was better following TAVI. TAVI was however associated with a significant increase in the risk of major vascular complications and neurological adverse events including stroke.

The PARTNER trial used only the SAPIEN™ valve and excluded patients who were not eligible for TF implantation. The results may not therefore be generalisable to patients with severe peripheral vascular disease, or to other excluded subgroups such as patients requiring treatment of coronary stenosis. There is no published RCT evidence comparing other TAVI devices or non-TF implantation routes with medical management in inoperable patients, and no ongoing trials were identified.

TAVI technology has advanced since the PARTNER trial was conducted and rapid progress is being made in device modification. 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.

The UK TAVI registry is still at an early stage of development. Data collated so far in this and other prospective European registries indicate better mortality outcomes among patients who are eligible for TF implantation. The registry data also indicate differences in outcomes among TAVI devices, such as the higher incidence of clinically important paravalvular regurgitation and requirement for new pacemaker implantation with CoreValve compared with SAPIEN devices.

There is currently limited published information on the durability of implanted TAVI devices because few studies have reported sufficient long-term follow up.

A large body of evidence from mostly uncontrolled observational studies of uncertain quality has been summarised in the secondary literature. Large meta-analyses that combined TAVI outcomes from heterogeneous studies were not included in this evidence note because, in the absence of a comparator, they are not useful

for comparing TAVI with standard care, and the pooled effect estimates cannot be generalised to any particular patient group, TAVI device or implantation route.

Regarding the cost effectiveness of TAVI for this patient group, there is evidence to support the cost effectiveness of TAVI relative to medical management. However, the evidence must be considered in light of the uncertainties highlighted in this report.

TAVI in Scotland

Unpublished preliminary data obtained from the Scottish specialist centre are summarised in Table 3 (N Uren, Consultant Cardiologist/Clinical Director for Cardiac Services, Royal Infirmary of Edinburgh. D Sorensen, CTR Data Manager. Personal Communication, 18 Feb 2014). The centre provided TAVI to 75 patients between 12 October 2012 and 17 January 2014: 49 procedures were TF, 24 TAo and 2 TA. TAVI was performed with the Edwards SAPIEN XT™ and SAPIEN™ devices.

Patients are typically followed-up by the referring hospital 3 months post-procedure. As patients are not routinely followed up by the specialist centre, follow-up information on events other than major events at any time point following hospital discharge can be uneven (N Uren, Consultant Cardiologist/Clinical Director for Cardiac Services, Royal Infirmary of Edinburgh. Personal Communication, 18 Feb 2014). Sufficient data are not yet available to estimate the rate of mortality at 1 year.

Table 3 Scottish specialist centre for TAVI summary data

Cases	All (n=75)	TF (n=49)	TAo (n=24)	TA (n=2)
Mean (median, range) logistic EuroSCORE	26.6 (25.8; 2.2 to 59.9)	23.9 (22.1; 2.2 to 59.9)	32.8 (31.8; 8.4 to 57.0)	18.6 (18.6; 16.9 to 20.4)
Median (days) (range) length of hospital stay	4 (0 to 37)	4 (0 to 17)	6 (3 to 37)	4 (4 to 4)
Median (days) (range) length of stay in ITU/ HDU	1 (0 to 31)	1 (0 to 15)	2 (1 to 31)	1.5 (1 to 2)
Median (days) (range) length of stay on ward	2 (0 to 15)	2 (0 to 14)	3 (0 to 15)	2.5 (2 to 3)
Success rate (no death/ stroke/MI to 30 days)	91% (68/75)	90% (44/49)	92% (22/24)	100% (2/2)
In-hospital mortality	5.3% (4/75)	6.1% (3/49)	4.2% (1/24)	0% (0/2)
30-day mortality including in-hospital	5.3% (4/75)	6.1% (3/49)	4.2% (1/24)	0% (0/2)
Death/stroke/MI after 30 days	9.3% (7/75)	10.2% (5/49)	8.3% (2/24)	0% (0/2)
Conversion to full sternotomy	2.7% (2/75)	2.0% (1/49)	4.2% (1/24)	0% (0/2)
Bailout PCI	2.7% (2/75)	2.0% (1/49)	4.2% (1/24)	0% (0/2)
Periprocedural MI	1.3% (1/75)	0% (0/49)	4.2% (1/24)	0% (0/2)
Major vascular complications (requiring surgery)	2.7% (2/75)	4.1% (2/49)	0% (0/24)	0% (0/2)
CVA up to discharge	2.7% (2/75)	2.0% (1/49)	4.2% (1/24)	0% (0/2)
CVA from discharge up to 30 days	1.3% (1/75)	2.0% (1/49)	0% (0/24)	0% (0/2)
Aortic regurgitation (excluding mid/ trivalval/none)	2.7% (2/75)	2.0% (1/49)	4.2% (1/24)	0% (0/2)
Permanent pacing	8.0% (6/75)	8.2% (4/49)	8.3% (2/24)	0% (0/2)
Bleeding (non-major)	8.0% (6/75)	10.2% (5/49)	4.2% (1/24)	0% (0/2)

PCI: percutaneous coronary intervention; CVA: cerebrovascular accidents

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The evidence note process has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on

www.healthcareimprovementscotland.org

About evidence notes

This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For further information about the evidence note process see

http://www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email evidencenotes.HCIS@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network

<http://www.knowledge.scot.nhs.uk>, or by contacting your local library and information service.

Acknowledgements

Healthcare Improvement Scotland and the Scottish Health Technologies Group (SHTG) invited the following individuals and organisations to peer review the draft evidence note:

- National Planning Forum TAVI Clinical Oversight Group, Independent topic reviewers
- Dr Margaret McEntegart, Consultant Interventional Cardiologist, NHS Greater Glasgow and Clyde, Clinical expert
- Dr Philip Adamson, Interventional Fellow, Royal Infirmary of Edinburgh, Independent topic reviewer
- Professor Adrian Banning, Consultant Cardiologist on behalf of the British Cardiovascular Society, Independent topic reviewer
- Dr Nick Cruden, Consultant Cardiologist, NHS Lothian, Independent topic reviewer
- Dr Jonathan Howell, Consultant in Public Health and Lead Clinician for TAVI in England, NHS England, Independent topic reviewer
- Boston Scientific, Edwards Life Sciences and Medtronic, Manufacturer of technology

Declarations of interest were sought from all peer reviewers. All contributions from peer reviewers were considered by the group. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

Healthcare Improvement Scotland development team

- Heather McIntosh, Lead Author/Health Services Researcher
- Edward Clifton, Author, Senior Health Economist
- Jenny Harbour, Information Scientist
- Susan Downie, Medical Writer
- Emma Riches, Medical Writer
- Marina Tudor, Team Support Administrator
- Members of the SHTG evidence review committee

© Healthcare Improvement Scotland 2014



NICE has accredited the process used by Healthcare Improvement Scotland to produce its evidence review products. Accreditation is valid for 5 years from January 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation

References

1. Healthcare Improvement Scotland. Transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis in adults [online]. 2011 [cited 2014 Apr 17]; Available from: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/earlier_evidence_notes/evidence_note_38.aspx.
2. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, *et al*. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24(13):1231–43.
3. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, *et al*. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J*. 2005;26(24):2714–20.
4. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, *et al*. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modelling study. *J Am Coll Cardiol*. 2013;62(11):1002-12.
5. Sethi S, Daniel T, Howell J, Griffin C. A commissioning framework for transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis. 2009 [cited 2014 Apr 17]; Available from: <http://www.bcis.org.uk/resources/documents/TAVI%20National%20Commissioning%20Framework%20FINAL%20160309.pdf>
6. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, *et al*. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33(19):2451–96.
7. NHS Commissioning Board. Clinical commissioning policy: transcatheter aortic valve implantation (TAVI) for aortic stenosis. 2013 [cited 2014 Apr 17]; Available from: <http://www.england.nhs.uk/wp-content/uploads/2013/04/a09-p-a.pdf>
8. Del Valle-Fernández R, Martínez CA, Ruiz CE. Transcatheter aortic valve implantation. *Cardiol Clin*. 2010;28(1):155–68.
9. Webb JG, Wood DA. Current status of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2012;60(6):483-92.
10. ECRI. Transcatheter aortic valve implantation for treating aortic stenosis: health technology forecast. Plymouth Meeting, PA: ECRI; 2012.
11. Bande M, Michev I, Sharp AS, Chieffo A, Colombo A. Percutaneous transcatheter aortic valve implantation: past accomplishments, present achievements and applications, future perspectives. *Cardiol Rev*. 2010;18(3):111-24.
12. ECRI. Transcatheter versus surgical aortic valve replacement for treating severe aortic stenosis: hotline response. Plymouth Meeting, PA: ECRI; 2013.
13. ECRI. Transcatheter aortic valve implantation using the Sapien valve for treating severe aortic valve stenosis: emerging technology evidence report. Plymouth Meeting, PA: ECRI; 2013.
14. Ludman PF, UK TAVI Steering Group, National Institute for Cardiovascular Outcomes Research. The UK transcatheter aortic valve implantation registry; one of the suite of registries hosted by the National Institute for Cardiovascular Outcomes Research (NICOR). *Heart*. 2012;98(24):1787-9.

References continued

15. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, *et al.* Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the UK TAVI (United Kingdom Transcatheter Aortic Valve Implantation) registry. *J Am Coll Cardiol.* 2011;58(20):2130-8.
16. NICE. Transcatheter aortic valve implantation for aortic stenosis. Interventional procedure guidance 421. 2012 [cited 2014 Apr 17]; Available from: <http://www.nice.org.uk/nicemedia/live/11914/58611/58611.pdf>
17. di Marco F, Gerosa G. Percutaneous aortic valve replacement: which patients are suitable for it? A quest for a controlled use. *J Thorac Cardiovasc Surg.* 2007;133(2):294-8.
18. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, *et al.* Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363(17):1597-607.
19. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, *et al.* Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med.* 2012;366(18):1696-704.
20. Belgian Health Care Knowledge Centre (KCE). Transcatheter aortic valve implantation (TAVI): a health technology assessment update. 2011 [cited 2014 Apr 17]; Available from: <http://kce.fgov.be/publication/report/transcatheter-aortic-valve-implantation-tavi-a-health-technology-assessment-updat>
21. Neyt M, Van Brabandt H. TAVI: reveal the truth, the whole truth, and nothing but the truth. *J Med Econ.* 2013;16(5):581-5.
22. Food and Drug Administration. The Edwards SAPIEN® THV transcatheter heart valve system for patients with severe aortic stenosis who are not candidates for conventional open-heart aortic valve replacement surgery. 2011 [cited 2014 Apr 17]; Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM262935.pdf>
23. Thomas M. The FDA panel meeting to discuss transcatheter aortic valve implantation: a first-hand European perspective. 2011 [cited 2014 Apr 17]; Available from: http://bmctoday.net/citoday/pdfs/cit0811_fda.pdf
24. Svensson LG, Tuzcu M, Kapadia S, Blackstone EH, Roselli EE, Gillinov AM, *et al.* A comprehensive review of the PARTNER trial. *J Thorac Cardiovasc Surg.* 2013;145(3 Suppl):S11-6.
25. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, *et al.* Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol.* 2014. DOI: 10.1016/j.jacc.2014.02.556
26. NICE. Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis. 2011 [cited 2014 Apr 17]; Available from: <http://www.nice.org.uk/nicemedia/live/11914/39663/39663.pdf>
27. Sehatzadeh S, Doble B, Xie F, Blackhouse G, Campbell K, Kaulback K, *et al.* Transcatheter aortic valve implantation (TAVI) for treatment of aortic valve stenosis: an evidence update. 2013 [cited 2014 Apr 17]; Available from: <http://www.hqontario.ca/Portals/0/Documents/eds/ohtas/report-tavi-aortic-valve-stenosis-130516-en.pdf>

References continued

28. Canadian Agency for Drugs and Technologies in Health. Transcatheter aortic valve replacement in severe aortic stenosis: a review of comparative durability and clinical effectiveness beyond 12 months. 2013 [cited 2014 Apr 17]; Available from: http://www.cadth.ca/media/pdf/RD0029_TAVR_e.pdf
29. Sinclair A, Xie X, McGregor M. Transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis. 2013 [cited 2014 Apr 17]; Available from: https://secureweb.mcgill.ca/tau/sites/mcgill.ca/tau/files/muhc_tau_2013_70_tavi.pdf
30. Tice JA. Transcatheter aortic valve replacement in patients with severe aortic stenosis who cannot undergo surgery. 2012 [cited 2014 Apr 17]; Available from: http://www.ctaf.org/sites/default/files/assessments/1426_file_TAVR_F2012.pdf
31. Figulla L, Neumann A, Figulla HR, Kahlert P, Erbel R, Neumann T. Transcatheter aortic valve implantation: evidence on safety and efficacy compared with medical therapy: a systematic review of current literature. *Clin Res Cardiol*. 2011;100(4):265-76.
32. Messori A, Trippoli S, Biancari F. Early and intermediate survival after transcatheter aortic valve implantation: systematic review and meta-analysis of 14 studies. *BMJ Open*. 2013;3(1):e001770.
33. Eggebrecht H, Schmermund A, Voigtländer T, Kahlert P, Erbel R, Mehta RH. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. *EuroIntervention*. 2012;8(1):129-38.
34. Erkapic D, De Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohnloser SH. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. *J Cardiovasc Electrophysiol*. 2012;23(4):391-7.
35. Généreux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, *et al*. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol*. 2012;59(25):2317-26.
36. Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, *et al*. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol*. 2013;61(15):1585-95.
37. Khatri PJ, Webb JG, Rodés-Cabau J, Fremes SE, Ruel M, Lau K, *et al*. Adverse effects associated with transcatheter aortic valve implantation: a meta-analysis of contemporary studies. *Ann Intern Med*. 2013;158(1):35-46.
38. Eggebrecht H, Schmermund A, Kahlert P, Erbel R, Voigtländer T, Mehta RH. Emergent cardiac surgery during transcatheter aortic valve implantation (TAVI): a weighted meta-analysis of 9,251 patients from 46 studies. *EuroIntervention*. 2013;8(9):1072-80.
39. Rahnavardi M, Santibanez J, Sian K, Yan TD. A systematic review of transapical aortic valve implantation. *Ann Cardiothorac Surg*. 2012;1(2):116-28.
40. Blackman DJ, Baxter PD, Gale CP, Moat NE, Maccarthy PA, Hildick-Smith D, *et al*. Do outcomes from transcatheter aortic valve implantation vary according to access route and valve type? The UK TAVI Registry. *J Interv Cardiol*. 2014;27(1):86-95.
41. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, *et al*. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2011;124(4):425-33.

References continued

42. Wendler O, Walther T, Schroefel H, Lange R, Treede H, Fusari M, *et al.* Transapical aortic valve implantation: mid-term outcome from the SOURCE registry. *Eur J Cardiothorac Surg.* 2013;43(3):505-11; discussion 511-2.
43. D'Onofrio A, Salizzoni S, Agrifoglio M, Cota L, Luzi G, Tartara PM, *et al.* Medium term outcomes of transapical aortic valve implantation: results from the Italian Registry of Trans-Apical Aortic Valve Implantation. *Ann Thorac Surg.* 2013;96(3):830-6.
44. Di Mario C, Eltchaninoff H, Moat N, Goicolea J, Ussia GP, Kala P, *et al.* The 2011-12 pilot European Sentinel Registry of Transcatheter Aortic Valve Implantation: in-hospital results in 4,571 patients. *EuroIntervention.* 2013;8(12):1362-71.
45. Reynolds MR, Magnuson EA, Wang K, Lei Y, Vilain K, Walczak J, *et al.* Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). *Circulation.* 2012;125(9):1102-9.
46. Reynolds MR, Magnuson EA, Lei Y, Leon MB, Smith CR, Svensson LG, *et al.* Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. *Circulation.* 2011;124(18):1964-72.
47. Gilard M, Eltchaninoff H, Lung B, Donzeau-Gouge P, Chevreul K, Fajadet J, *et al.* Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med.* 2012;366(18):1705-15.
48. D'Onofrio A, Rubino P, Fusari M, Salvador L, Musumeci F, Rinaldi M, *et al.* Clinical and hemodynamic outcomes of "all-comers" undergoing transapical aortic valve implantation: results from the Italian Registry of Trans-Apical Aortic Valve Implantation (I-TA). *J Thorac Cardiovasc Surg.* 2011;142(4):768-75.
49. Wendler O, Walther T, Schroefel H, Lange R, Treede H, Fusari M, *et al.* The SOURCE Registry: what is the learning curve in trans-apical aortic valve implantation? *Eur J Cardiothorac Surg.* 2011;39(6):853-9; discussion 859-60.
50. Tice JA. Transcatheter aortic valve replacement in patients with severe aortic stenosis who are at high risk for surgical complications. 2013 [cited 2014 Apr 17]; Available from: http://www.ctaf.org/sites/default/files/assessments/TAVR_HighRisk%20Mar%202013.pdf
51. Toggweiler S, Humphries KH, Lee M, Binder RK, Moss RR, Freeman M, *et al.* 5-year outcome after transcatheter aortic valve implantation. *J Am Coll Cardiol.* 2013;61(4):413-9.
52. Gurvitch R, Wood DA, Leipsic J, Tay EL, Ye J, Lichtenstein SV, *et al.* Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. *Circulation.* 2010;122(13):1319-27.
53. Gerckens U, Schuler G, Bonan R, Den Heijer P, Serruys P, Bosmans J, *et al.* Four-year durability and patient survival with CoreValve transcatheter aortic valve. *Eur Heart J.* 2011;32(Suppl 1):169.
54. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, *et al.* Thirty-day results of the SAPIEN aortic bioprosthesis European outcome (SOURCE) registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation.* 2010;122(1):62-9.
55. Bosmans JM, Kefer J, De Bruyne B, Herijgers P, Dubois C, Legrand V, *et al.* Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: results of the Belgian national registry. *Interact Cardiovasc Thorac Surg.* 2011;12(5):762-7.

References continued

56. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, *et al*. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57(3):253-69.
57. Ghanbari H, Kidane AG, Burriesci G, Bonhoeffer P, Seifalian AM. Percutaneous heart valve replacement: an update. *Trends Cardiovasc Med*. 2008;18(4):117-25.
58. Watt M, Mealing S, Eaton J, Piazza N, Moat N, Brasseur P, *et al*. Cost-effectiveness of transcatheter aortic valve replacement in patients ineligible for conventional aortic valve replacement. *Heart*. 2012;98(5):370-6.
59. Murphy A, Fenwick E, Toff WD, Neilson MP, Berry C, Uren N, *et al*. Transcatheter aortic valve implantation for severe aortic stenosis: the cost-effectiveness case for inoperable patients in the United Kingdom. *Int J Technol Assess Health Care*. 2013;29(1):12-9.
60. Orlando R, Pennant M, Rooney S, Khogali S, Bayliss S, Hassan A, *et al*. Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: a model-based economic evaluation. 2013 [cited 2014 Apr 17]; Available from: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0009/76815/FullReport-hta17330.pdf
61. Neyt M, Van Brabandt H, Devriese S, Van De Sande S. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. *BMJ Open*. 2012;2(3):e001032.
62. Simons CT, Cipriano LE, Shah RU, Garber AM, Owens DK, Hlatky MA. Transcatheter aortic valve replacement in nonsurgical candidates with severe, symptomatic aortic stenosis: a cost-effectiveness analysis. *Circ Cardiovasc Qual Outcomes*. 2013;6(4):419-28.
63. Hancock-Howard RL, Feindel CM, Rodes-Cabau J, Webb JG, Thompson AK, Banz K. Cost effectiveness of transcatheter aortic valve replacement compared to medical management in inoperable patients with severe aortic stenosis: Canadian analysis based on the PARTNER trial cohort B findings. *J Med Econ*. 2013;16(4):566-74.
64. Doble B, Blackhouse G, Goeree R, Xie F. Cost-effectiveness of the Edwards SAPIEN transcatheter heart valve compared with standard management and surgical aortic valve replacement in patients with severe symptomatic aortic stenosis: a Canadian perspective. *J Thorac Cardiovasc Surg*. 2013;146(1):52-60.
65. Neyt M, Van Brabandt H. Cost-effectiveness of transcatheter aortic valve replacement: overoptimistic study results and a call for publication of complete trial results. *Heart*. 2012;98(13):1031-3; author reply 1033-4.
66. Van Brabandt H, Neyt M, Hulstaert F. Transcatheter aortic valve implantation (TAVI): risky and costly. *BMJ*. 2012;345:e4710.
67. Reynolds M, Thompson A, Duhay F. Correction of faulty assumptions in cost-effectiveness analysis. *J Thorac Cardiovasc Surg*. 2013;145(1):308-9.