Introduction

This Evidence Note was undertaken to inform the work of the National Planning Forum subgroup on TAVI. This Evidence Note includes the recently published results from the PARTNER randomised controlled trial (cohort A) which reported on transcatheter versus surgical aortic-valve replacement in high-risk surgical patients. This Evidence Note will be reviewed again following publication of the National Institute for Health Research HTA on the cost effectiveness of TAVI for aortic stenosis in patients who cannot undergo surgery.

Health technology description

Surgical aortic valve replacement (AVR) is the current standard treatment for patients with severe symptomatic aortic stenosis (AS)\(^1\,^2\). Transcatheter aortic valve implantation (TAVI) is a minimally invasive procedure in which a bioprosthetic replacement valve is delivered percutaneously through the vascular system inside a catheter. Transcatheter access to the aortic valve is achieved mainly by the retrograde transfemoral (TF), transapical (TA) or transaxillary/subclavian routes\(^1\,^3\). The TA and transaxillary/subclavian routes have developed as alternative approaches for patients with peripheral vascular disease that precludes femoral access. The TA procedure involves a mini-thoracotomy to gain access to the aortic valve through the apex of the left ventricle and hence is not strictly percutaneous.

TAVI devices and delivery systems have developed rapidly since the first in-man procedure was reported in 2002. The devices with current European CE mark approval are the balloon-expandable Edwards SAPIEN™ and SAPIEN XT™ bovine pericardium tissue valves (Edwards Lifesciences Inc, Irving, CA) and the self-expanding Medtronic porcine pericardium tissue CoreValve® ReValving system (Medtronic, Minneapolis, MN). The Edwards SAPIEN™ valves can be implanted using the retrograde TF or the TA approach, and CoreValve® devices by the retrograde TF or transaxillary/subclavicular arterial route. At least 20 other devices have been identified as being in various stages of development\(^1\,^3\,^4\).

TAVI has been advocated for the treatment of patients who are unsuitable for conventional AVR as the risks of surgery are unacceptably high because of advanced age, frailty and/or the presence of cardiac or non-cardiac co-morbidities. The current alternative for these patients is palliative medical management with or without balloon aortic valvuloplasty (BAV), although BAV is not commonly performed in Scotland\(^1\,^3\,^5\). TAVI may also represent a replacement technology as a possible alternative to conventional AVR surgery for a wider patient group\(^6\). The long-term durability of bioprosthetic percutaneous prosthetic valves, which are susceptible to

Key points

- In the only randomised controlled trial (RCT) (PARTNER 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.
- In the only RCT (PARTNER cohort A), TAVI was not inferior to surgical aortic valve replacement with respect to death from any cause after 1 year in candidates for surgery who were at high risk of increased operative complications and death.
- In the RCT, TAVI was associated with a significantly higher incidence of major vascular complications and neurological adverse events, in both cohorts A and B.
- There are limited published data on TAVI outcomes beyond 1 year of follow up.
- There is limited information on the impact of TAVI on quality of life compared with alternative interventions.
- There are currently no published evaluations of the cost effectiveness of TAVI.
- Patient selection for TAVI should be undertaken by a multidisciplinary team.
degeneration, calcification and inflammation, is of particular concern when the indication for TAVI extends to lower-risk patients with longer life expectancy\(^1,5\). TAVI is not currently available in Scotland.

**Epidemiology**

AS is the most common native heart valve disease in adults in Europe\(^7\). In most cases, the aetiology is degenerative hence it is most often seen in the elderly, increasing with age due to degenerative calcification\(^7,8\). 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. Without intervention, patients with severe symptomatic AS have a poor prognosis with an average survival of 2–3 years\(^9\).

It has been estimated that more than one third of elderly patients with severe symptomatic AS in Europe are not referred for surgical AVR\(^8\). 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 co-morbidities\(^8\). Coronary heart disease is a frequent co-morbidity in the elderly and the risk of surgical mortality is higher among patients who undergo concurrent coronary artery bypass graft (CABG) and valve surgery compared with valve surgery alone\(^10\). The UK cardiac surgical register of procedures performed in NHS hospitals, including units in Scotland, recorded 17,797 isolated AVR procedures and 12,646 combined AVR and CABG procedures in 2004–2008\(^11\). In that period, 64.5% of isolated AVR implants were bioprosthetic valves\(^11\). Information Services Division recorded 867 surgical AVR procedures in NHS hospitals in Scotland in 2009\(^11\). The UK TAVI registry recorded 862 TAVI procedures in England between January 2007 and December 2009\(^12\).

**Patient selection**

Patient eligibility for TAVI in the UK has been estimated at between 16 per million and 21 per million population, the former representing around 80 procedures per year in Scotland\(^6\). 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 \(\geq 10\)%\(^1\). The ability of these scoring systems alone to accurately predict surgical risk in patients undergoing AVR, or to select patients for TAVI, is limited\(^3,13\). Patient selection for TAVI remains largely determined by clinical judgement on an individual patient basis and should, therefore, be undertaken by a multidisciplinary team including a cardiologist, cardiac surgeon and cardiac anaesthetist\(^2\).

**Clinical effectiveness**

Published data are available from one RCT, the multicentre PARTNER (Placement of Aortic Transcatheter Valves) trial sponsored by Edwards Lifesciences\(^14,15\). The trial recruited patients at 22 sites in the USA, 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\(^\text{TM}\) valve or surgical AVR (cohort A)\(^15\) while those who were considered not to be suitable candidates for surgery were randomised to TAVI or medical management (usually BAV) (cohort B)\(^14\). The exclusion criteria included coronary artery disease requiring revascularisation, severe renal insufficiency, and life expectancy <12 months due to non-cardiac co-morbid conditions. The trial appears to have been generally well conducted, although it is unclear from the trial reports that adequate steps were taken to minimise selection bias. A large body of evidence from published and unpublished TAVI case series and registry data has been summarised in five technology assessments\(^4,16-19\), and three systematic reviews\(^20-22\). Data from the UK TAVI registry have been published subsequently\(^12\).

**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 \(\geq 10\)\(^15\). 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 (ie 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% Confidence Interval (CI)\(^15\).

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 retrograde, 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). 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, and one patient allocated to AVR underwent TA TAVI.

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 non-inferiority of TAVI compared with AVR (p=0.001 for non-inferiority). TAVI was associated with a statistically significantly shorter length of stay in an intensive care unit (ICU) (3 days versus 5 days; p<0.001) and index hospital stay (8 days versus 12 days; p<0.001). There was no statistically significant difference between TAVI and AVR with respect to repeat hospitalisation at 30 days (p=0.64) or 1 year (p=0.38), or in cardiac symptoms (NYHA functional class ≤II) or 6 minute walk test distance among evaluable patients at 1 year. Quality of life (QOL) outcomes have not been published.

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 co-existing conditions precluded surgery on the basis of a predicted ≥50% probability of surgical mortality at 30 days or serious irreversible morbidity. Patients found to have severe peripheral vascular disease that precluded TF access were excluded. The main primary outcome was all-cause mortality (Kaplan-Meier analysis). The median duration of follow up was 1.6 years (range 1.0 to 2.8). Analysis was by intention-to-treat for effectiveness outcomes and ‘as treated’ for adverse events.

Of the 358 patients recruited to cohort B, 179 were allocated to TF retrograde TAVI and 179 to medical management, of whom 150 (83.8%) underwent BAV. The mean age of patients in both groups was 83 years (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). 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 measurement.

All-cause mortality at 1 year 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). 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)). Repeat hospitalisation due to AS or complications of the valve procedure was also significantly lower in the TAVI group at 1 year (22.3% versus 44.1%; p<0.001). A significantly higher proportion of survivors in the TAVI group (74.8%) compared with the control group (42.0%) were asymptomatic at 1 year or had mild symptoms defined as NYHA functional class I or II (p<0.001). 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 group. Unpublished data on QOL among survivors eligible for assessment showed a statistically significant difference in Kansas City Cardiomyopathy Questionnaire summary scores (primary outcome) up to 1 year in favour of TAVI (p<0.001).

Non-randomised studies

International TAVI registries have reported procedural success rates of 87.3% to 98.2% for the TF retrograde approach and 87.5% to 98.3% using the TA approach. The UK TAVI registry recently reported a 98.8% success rate overall using Edwards SAPIEN™ and CoreValve® devices implanted by retrograde TF and other routes. The mean length of hospital stay ranged from 7 to 17 days in 12 published case series from Europe and Canada. SOURCE registry data from 10 European countries indicated an average length of hospital stay of 9.5 days (range 6.5 to 11.4) following TF TAVI and 11.4 days (range 5.2 to 12.9) for TA implantation. The average length of stay in ICU was 2.8 days and 3.5 days, respectively. One-year mortality rates ranged from 20% to 35% in TF retrograde series and 34% to 45.3% in TA series. The UK TAVI registry (Kaplan-Meier analysis) reported 82.4% survival in the TF group at 1 year and 78.3% at 2 years compared with 75.5% and 66.5%, respectively, for other routes (p=0.017). The longest follow up data to be published are from a Canadian single-centre patient series that showed 61%
survival at 3 years among high risk patients who were unsuitable for surgery and who underwent TF or TA TAVI and survived past 30 days (n=70)\textsuperscript{25}; and 58% (SD 9.5) overall survival to 3 years among a larger cohort of TA TAVI patients (n=71)\textsuperscript{26}. Four case series that used various generic instruments to measure QOL in TAVI patients have reported statistically significant improvements in some domains, however without control groups the observed benefits cannot be directly compared with surgical AVR or medical management\textsuperscript{27-30}. 

Safety

PARTNER trial cohort A

The PARTNER trial found a 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%; \(p=0.07\)) but not in the as-treated analysis (5.2% versus 8.0%; \(p=0.15\))\textsuperscript{15}. Major vascular complications were significantly more common in the TAVI group compared with AVR at 30 days (11.0% versus 3.2%; \(p<0.001\)) and 1 year (11.3% versus 3.5%; \(p<0.001\), as were neurological adverse events (comprising major and minor stroke and transient ischaemic attack) at 30 days (5.5% versus 2.4%; \(p=0.04\)) and 1 year (8.3% versus 4.3%, \(p=0.04\)). The rate of major strokes was 3.8% in the TAVI group versus 2.1% in the AVR group at 30 days (\(p=0.20\)) and 5.1% versus 2.4% (\(p=0.07\)) at 1 year. Major bleeding was significantly more common with AVR at both time points (19.5% versus 9.3% at 30 days and 25.7% versus 14.7% at 1 year; both \(p<0.001\)). There was no statistically significant difference in rates of myocardial infarction or acute kidney injury. Moderate or severe paravalvular aortic regurgitation was present in 11.8% of TAVI patients at 30 days and in 10.5% at 1 year. Valve embolisation occurred in one patient (0.6%), and three patients (1.7%) underwent a repeat TAVI procedure to treat clinically significant aortic regurgitation.

There was no statistically significant difference in the number of patients requiring a new pacemaker at 30 days or 1 year\textsuperscript{14}.

Non-randomised studies

International registries and case series have reported 30-day mortality rates ranging from 6.4% to 25%, with higher procedure-related mortality rates reflecting higher surgical risk scores in TA cohorts compared with TF implantation\textsuperscript{4,16,18,21,31,32}. Similarly, analysis of UK TAVI registry data showed 94.8% survival to 30 days in the TF group with a mean logistic EuroSCORE of 20.3% compared with 89.1% survival and a mean logistic EuroSCORE of 24.5% in the other routes group (\(p<0.01\))\textsuperscript{12}. Complication rates observed in TAVI patient series varied widely. Vascular complications occurred especially with the TF approach, with an incidence of 10–15%, and stroke occurred in around 3–10% of cases\textsuperscript{4,12,31,33}. New permanent pacemaker implantation was required by 7% of Edwards SAPIEN™ and 26% of Medtronic CoreValve® recipients reported to the UK registry\textsuperscript{12}, similar to rates recorded in other registries\textsuperscript{31,33}. Few studies have published data on the durability of implanted valves beyond 1 year: a Canadian patient series (n=70) with a median follow up of 3.7 years (interquartile range 3.4 to 4.3) reported no cases of structural deterioration of Edwards SAPIEN™ valves at 3 years\textsuperscript{25}.

Cost effectiveness

Currently, there are no published evaluations of the cost effectiveness of TAVI compared with surgical AVR or medical management\textsuperscript{4,16,18}. Several unpublished developmental economic models that were identified have important limitations.
Equality and Diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the six equality groups defined by age, disability, gender, race, religion/belief 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

For further information about the Evidence Note process, see www.healthcareimprovementscotland.org

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.

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- Marina Logan, Team Support Administrator

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References continued


* NICE are currently updating this interventional procedure guidance with an anticipated publication date of November 2011.