

Transcatheter aortic valve implantation: new hope in the management of valvular heart disease

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ABSTRACT

Severe calcific aortic stenosis is relatively common, and unless treated with valve replacement it carries an adverse prognosis. A large number of patients, however, are denied surgery due to their advanced age or coexistent medical conditions that increase perioperative cardiovascular risks. Transcatheter aortic valve implantation (TAVI), a technique in which a bioprosthetic valve is inserted via a catheter and implanted within the diseased native aortic valve, is a new therapeutic modality for treatment of older patients with severe symptomatic aortic stenosis and other comorbidities, who have an inherently high surgical risk. This review will provide an overview of the pivotal trials in the development of TAVI; while also investigating important complications and limitations of the procedure and evaluating how new valves are being designed and clinically evaluated, with the ultimate goal of reducing potential complications and expanding the use of TAVI to lower-risk patient cohorts.

INTRODUCTION

Calcific aortic valve disease is relatively common in the high-income countries, affecting between 4% and 5% of adults above the age of 75 years, and unless corrected, it carries significant morbidity and mortality.^{1 2} It has an insidious course with a long latent period followed by a rapid progression leading to symptoms of breathlessness, chest pain and syncope.^{3 4} It is an important cause of congestive and sometimes intractable heart failure and of sudden cardiac death.

Traditional surgical valve replacement has been the mainstay in the treatment of severe aortic valvular disease, and in the absence of serious comorbidities it is associated with low operative mortality.⁵ However, a large number of patients (estimated at 30%–40%) are denied surgery due to their advanced age, impaired left ventricular systolic function and/or coexistent comorbidities that increase the perioperative cardiovascular risks.^{6 7}

Percutaneous balloon valvuloplasty was the first catheter-based modality to address this problem.⁸ However, early data had suggested high restenosis rates and only marginal improvement in the clinical outcomes. Therefore, balloon valvuloplasty remains an emergency option as a bridge to aortic valve surgery. Transcatheter aortic valve implantation (TAVI), a technique in which a bioprosthetic valve is inserted via a catheter and implanted within the diseased native aortic valve, was first implanted by Andersen in 1993 in a closed chest experimental pig model.⁹ It was a true ‘resurrection’ for Cribier and his whole team performing the first TAVI in an inoperable patient in 2002^{10 11} using a transeptal

antegrade approach and balloon-expandable aortic valve prosthesis, while at the same time in the USA, animal studies were being carried out to develop a transapical method of implantation. This was followed by the development of a retrograde transfemoral technique, which carried a lower risk of stroke.¹² This became feasible following development of a catheter that could be flexed to get around the aortic arch and across the aortic valve. The initial success rates have led to a rapid adoption of this technique in clinical practice in high-risk patients with severe symptomatic aortic stenosis. Since 2012, TAVI has been performed in more than 50 000 patients worldwide and a number of different aortic prostheses have since been developed.

Currently, two valve models are available: the Edwards SAPIEN valve and the Medtronic CoreValve. The Edwards SAPIEN valve consists of trileaflet bovine-pericardium valve mounted on a balloon-expandable stainless steel stent, and is available in four sizes (20, 23, 26 and 29 mm). It can be implanted in native annuli with diameters of 16–27 mm. The CoreValve has an autoexpandable nitinol stent containing a porcine pericardial valve, is available in three sizes (26, 29 and 31 mm) and can be implanted in native annuli ranging from 20 to 29 mm. A second generation of TAVI devices are currently being evaluated and demonstrate good results.¹³

INDICATIONS

TAVI is currently indicated in patients with severe symptomatic aortic stenosis and acceptable life expectancy who are not suitable for aortic valve replacement (AVR) (indication class IB) or as an alternative to AVR in selected high-risk operable patients (class IIB), according to the ‘Heart Team’ assessment.¹⁴ The TAVI Heart Team comprised clinical cardiologists, interventionalists, surgeons, anaesthetists and imaging specialists with expertise in the treatment of valve disease, selects patients suitable for TAVI taking into account advantages and disadvantages of both surgical AVR and TAVI.

A logistic EuroSCORE $\geq 20\%$ or a Society of Thoracic Surgeons (STS) score $>10\%$ are suggested as indications for TAVI therapy. The logistic EuroSCORE tends to overestimate observed mortality risk by a factor of 2–3, and has led to development of a newly updated logistic EuroSCORE II that is currently available in clinical practice. Candidates for the TAVI procedure undergo comprehensive evaluation to assess the morphology of the native aortic valve and ascending aorta, peripheral arterial access and also for coexistent morbidity.



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CONTRAINDICATIONS

Multiple patient characteristics must be considered before deciding suitability for a TAVI, one of which is the underlying pathological process behind aortic stenosis. Currently, bicuspid aortic valve disease is considered a relative contraindication, and practically, it is mainly those with a calcified tricuspid aortic valve who are considered for the procedure. It is thought that the single-slit opening may not conform to the circular shape of the prosthesis. Furthermore, the ascending aorta and aortic root tend to be larger in this population, making sizing of the valve more difficult.

Despite these preliminary trials have shown the short-term outcome of a TAVI does not appear to be affected by the underlying pathological process behind aortic stenosis (whether that be senile calcification or congenital bicuspid valve), with complication rates not being significantly different between the two groups of patients. In the future, those with a bicuspid valve may also be considered for the procedure.¹⁵

Relative or absolute contraindications (box 1) for the above procedure include patients with sepsis including active endocarditis, recent myocardial infarction or stroke (within 30 days), left ventricular or atrial thrombus, moderate or severe mitral and tricuspid insufficiency, previous aortic mechanical or stented bioprosthesis, symptomatic carotid artery disease, aortic or aortoiliac vascular conditions that make access difficult, bleeding diathesis or coagulopathy, creatinine clearance <20 mL/min or active gastritis or bleeding. Independent predictors of long-term mortality include intrinsic patient characteristics such as diabetes mellitus, end-stage renal failure, preprocedural atrial fibrillation and chronic obstructive pulmonary disease. Along with the above contraindications, these should all be considered during patient selection and risk stratification.¹⁶

A number of subgroups require more precise evaluation, for example, transcatheter 'valve in a valve' appears as an attractive alternative in bioprosthesis failure with more than 100 successful TAVI-in-surgical aortic valve procedures already been

Box 1 Contraindications for transcatheter aortic valve implantation

Absolute contraindications

- ▶ Life expectancy <1 year
- ▶ Major comorbidities resulting in minor improvement of quality of life
- ▶ Disease of other valves with need for surgical treatment
- ▶ Inadequate annulus size (<18/>29 mm)
- ▶ Thrombus in left ventricle
- ▶ Active endocarditis
- ▶ Elevated risk of coronary ostium obstruction due to anatomical characteristics
- ▶ Plaques with mobile thrombi in the ascending aorta or arch
- ▶ For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)

Relative contraindications

- ▶ Bicuspid or non-calcified valves
- ▶ Coronary artery disease requiring revascularisation
- ▶ Haemodynamic instability
- ▶ Left ventricular ejection fraction <20%
- ▶ For transapical approach: severe pulmonary disease, left ventricular apex not accessible

performed.^{17 18} Several successful case reports document stenotic bicuspid aortic valves have been treated with TAVI and according to a German registry, 16% of patients with intermediate risk of surgery for aortic stenosis have chosen TAVI as a therapeutic regimen.¹⁹

THE PROCEDURE

A TAVI can be performed using various approaches with use of the transfemoral (TF) approach (figure 1) being most common. In some cases, this can be performed without the need for general anaesthesia and intubation. Other options include the subclavian or transapical (TA) approaches, which may be considered in patients with difficult femoral access due to calcification, tortuosity or small diameter vessels. The TA approach has the added benefit of allowing simultaneous procedures such as transcatheter mitral valve reimplantation and percutaneous coronary interventions to also occur. More recently, a transaortic approach has been described and has been associated with favourable outcomes.²⁰ Accurate positioning of the aortic prosthesis is of paramount importance. Once deployed the prosthesis cannot be retrieved. If the valve is positioned too high in

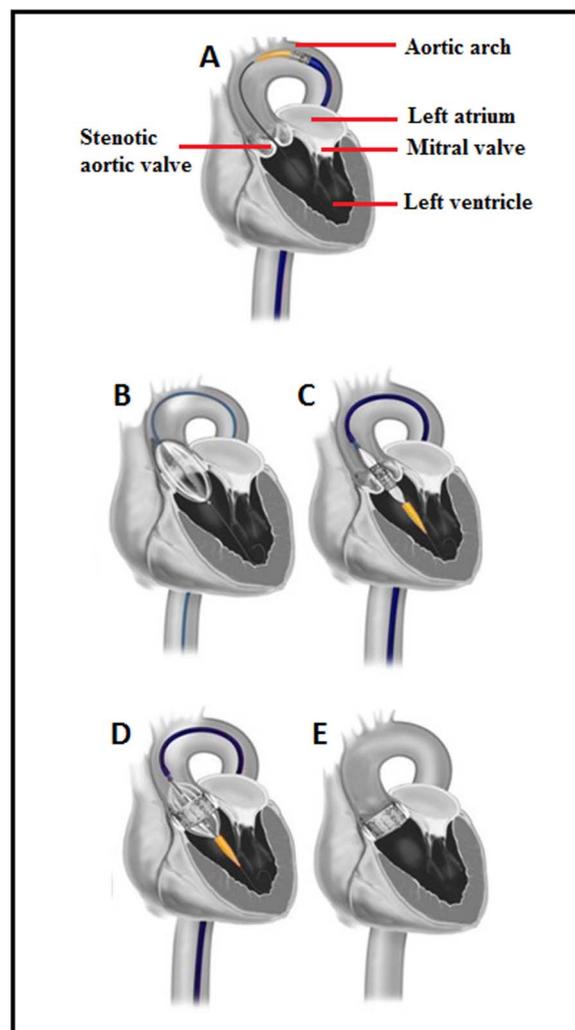


Figure 1 Transfemoral approach. (A) Valve delivery system is advanced via the femoral artery to the aortic arch. (B) Balloon expansion across the stenotic aortic valve. (C) Catheter system is advanced. (D) Valve is deployed. (E) Catheter system is removed with the valve in situ.

the aorta, it may embolise causing paravalvular regurgitation. Occlusion of the coronary artery ostia is a rare but life-threatening complication. Pharmacological therapy including heparin and prophylactic antibiotics during the procedure, and dual antiplatelet therapy (consisting of aspirin and clopidogrel) is recommended for at least 6 months, followed by lifelong aspirin (as this was the protocol used in clinical trials).¹³

The development of TAVI has been accompanied by recommendations of several cardiac societies for patient selection as well as for procedural outcome and follow-up data to a centrally based database for event tracking: British Cardiovascular Intervention Society, Society of Cardiothoracic Surgeons, European Society of Cardiology, American Heart Association, American College of Cardiology and German Cardiac Society.

PIVOTAL TAVI TRIALS

The PARTNER trial was a multicentre randomised clinical trial used to compare the use of TAVI against conventional medical and surgical therapies, for treatment of severe aortic stenosis. To date, it is the most definitive data set available.

Patients were divided into two cohorts. In cohort B patients were randomised to receive TAVI versus standard therapy (including balloon aortic valvuloplasty, which was performed in 83.8% of patients). The trial clearly demonstrated that use of TAVI had a significant morbidity and mortality benefit. These included a 1-year mortality (30.7% vs 50.7%; $p < 0.001$); the composite end point of death from any cause or repeat hospitalisation (42.5% vs 71.6%; $p < 0.001$), the rate of cardiac symptoms was significantly lower in the TAVI group (25.2% vs 58%; $p < 0.001$). However, the TAVI group was associated with increased incidence of major strokes (5.0% vs 1.1%; $p = 0.06$) and major vascular complications (16.2% vs 1.1%; $p < 0.001$), as compared with the group with standard therapy.¹³ Furthermore, the performance of the bioprosthetic valve was maintained with no deterioration after a year.

A further study was conducted on a second group of patients (known as cohort A), whereby patients were randomised to receive either conventional open-heart surgery or TAVI as treatment for their severe aortic stenosis. Those who received a TAVI were further randomised for either a TF or TA approach. Their preoperative baseline characteristics were well balanced. The rates of death were not significantly different, however, those randomised to the TAVI group had a significantly increased risk of a neurological event occurring (transient ischaemic attacks, minor and major strokes) compared with those in the surgical group at both 30 days (5.5% vs 2.4%; $p = 0.04$), and at 1 year (8.3% vs 4.3%; $p = 0.04$), but the rates of major stroke were not significantly different between the two groups. The transcatheter group also carried a higher rate of major vascular complications than surgical group (11.0% vs 3.2%; $p < 0.001$) but had lower rates of major bleeding events (9.3% vs 19.5%; $p < 0.001$) and new-onset atrial fibrillation (8.6% vs 16.0%; $p = 0.006$). At 30 days, patients in the TAVI group reported a greater improvement in symptoms and of those who could perform 6 min walk tests, patients in the TAVI group were able to walk further than those in the surgical group ($p = 0.002$). However, these differences were less noticeable at 1-year follow-up.²¹

The Medtronic CoreValve ADVANCE study²² was a large multicentre trial consisting of 1015 patients treated across 44 centres in 12 different countries. The study assessed the outcomes following the procedure using clinical end points defined by the Valve Academic Research Consortium.²³ These consisted of major adverse cardiovascular and cerebrovascular events (MACCE), and mortality. It demonstrated that in high-risk

patients (mean logistic EuroSCORE $19.4 \pm 12.3\%$), TAVI resulted in improved haemodynamics and aortic valve orifice area, with a low 30-day and 1-year MACCE rate, of 8.0% and 21.2%, respectively, and mortality rate at 12 months of 17.9% (which reported lower mortality rates in the PARTNER trial).

Subsequent analysis of health-related quality of life demonstrated a significant improvement at both 1 and 6 months compared with the baseline (baseline vs 1 vs 6 months) in both physical (32.82 vs 39.00 vs 39.74; $p < 0.001$) and mental summary scores (46.18 vs 48.51 vs 49.98; $p < 0.001$) and EQ-5D index (0.62 vs 0.72 vs 0.72; $p < 0.001$).²⁴ Three-year follow-up demonstrated an overall mortality of 33.7%, which was significantly lower in those with a STS score $\leq 7\%$, compared with those with a score $> 7\%$ (28.6 vs 45.9; $p < 0.01$). The study concluded TAVI should be recommended for those known to be high risk but with a STS score $\leq 7\%$.²⁵

These results demonstrated the effectiveness of the TAVI procedure, especially if carried out by experienced operators, with mortality rates and long-term outcomes improving as operators became more experienced.

MORBIDITY AND MORTALITY

Among patients treated with TAVI the in hospital and 30-day mortality was estimated to be around 8% and 12%, respectively,¹⁹ and the 1 year mortality at 25%.^{26–28} Severe complications include cerebral embolism, infection, pericardial tamponade, severe aortic regurgitation (AR), aortic dissection or cardiac rupture as well as the need for permanent pacemaker implantation for postprocedural advanced atrioventricular (AV) block.

More recent retrospective studies have shown a decline in both in-hospital mortality (3.5%), with cardiac death and stroke being the most common causes, and 1 year mortality (14.0%) and 5-year survival has also improved since the PARTNER trial from 28.2% in cohort A (where patients were randomised to receive either open heart surgery or TAVI) and 32.2% in cohort B (where patients were randomised to receive either balloon aortic valvuloplasty or TAVI), to 53.0% reported by the San Raffaele Scientific Institute in Milan and 47.0% from the UK TAVI registry. These findings are supported by a reduction in procedural complications. From 2007 to 2012, the incidence of stroke (an independent predictor of mortality) has declined from 3.6% to 2.4% ($p = 0.022$), and major vascular injury from 5.2% to 2.6% ($p < 0.0001$).^{16 29}

Recent publications have identified a number of baseline variables independently associated with mortality or poor outcome in patients undergoing TAVI (low body mass, functional status, left ventricular dysfunction, N-terminal probrain natriuretic peptide (NT-proBNP), prior stroke, diabetes, chronic kidney disease, anaemia, severe tricuspid and mitral regurgitation, porcelain aorta or history of chest radiation), which could be integrated into new scoring systems to quantify and predict the prognosis of TAVI both in the immediate and in the long term (box 2).³⁰

ACCESS SITE-RELATED COMPLICATIONS

The incidence and nature of complications varies depending on whether a TF or TA approach is used. TF is often preferred as it is less invasive, but it cannot be used if there is significant peripheral vascular disease, calcified or tortuous or small diameter vessels; in which case a TA approach would be used with the added benefit of not manipulating the aortic arch. Each has its own merits, although 30-day mortality is significantly higher in TA over TF ($p < 0.0001$) as is 1-year mortality if adjusted for

Box 2 Predictors of long-term mortality after TAVI

- ▶ Advanced age
 - ▶ Smoking
 - ▶ Logistic EuroSCORE
 - ▶ STS score
 - ▶ Calcium score
 - ▶ Baseline anaemia
 - ▶ Baseline renal failure, acute kidney injury
 - ▶ Pulmonary hypertension
 - ▶ Chronic obstructive pulmonary disease
 - ▶ Liver disease
 - ▶ Prior stroke
 - ▶ Major vascular complication
 - ▶ Myocardial injury
 - ▶ Systematic inflammatory response syndrome
 - ▶ Learning curve, early experience with TAVI
- STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

the patient's EuroSCORE (risk stratification model) ($p=0.0011$), thus making the TA approach an independent predictor of mortality. Despite this, the incidence of stroke, myocardial infarction and bleeding events is not significantly different. Due to the nature of TF, the incidence of major vascular events is understandably higher ($p<0.00001$).^{16 29 31}

Access site-related complications are largely related to the delivery catheters and the presence of coexistent aortoiliac atheromatous disease. These complications include dissection and perforation of the iliofemoral arteries leading to retroperitoneal haematoma and cardiogenic shock.

In an attempt to avoid the above complications vascular closure devices have been developed. These can be divided into suture-mediated devices such as Prostar or Proglide, and collagen-based devices such as Angioseal. Since their development, there has been increased success with the suture-mediated devices, with the Proglide device advancing from single to double suture deployment, thus creating an improved safety profile.^{32 33}

The most recently published trials have demonstrated the superiority of the Proglide device, with Prostar XL having a higher rate of major vascular complications (7.4% vs 1.9%; $p<0.001$),³⁴ an increased rate of closure device failure (19% vs 4.6%; $p<0.01$) and higher in-hospital mortality (5.9% vs 2.0%; $p=0.01$).³⁵

New haemostasis techniques have revolutionised the TAVI procedure, and along with the use of small catheters promise to significantly reduce both vascular and bleeding complications, and thus vastly improve the procedure safety profile.

POST-TAVI ATRIAL FIBRILLATION

The TA approach is also a strong predictor for the development of post-TAVI new-onset atrial fibrillation (NOAF), which occurs in 21% of patients undergoing the procedure, 50% of whom develop NOAF within the first 24 hours.³⁶

Interestingly, it was first thought that only pre-existing atrial fibrillation, and not NOAF, was associated with poor outcomes post-TAVI. Baseline atrial fibrillation is linked to a higher incidence of stroke, vascular complications and overall mortality and therefore should be taken into consideration during risk

stratification and when considering patient suitability for a TAVI.³⁷ Recent data also suggest that NOAF is a poor prognostic indicator and is associated with a borderline increase in 30-day mortality and a significant increase in 1-year mortality, when compared with those who remain in sinus rhythm. Whether this relationship is causal or not still demands further research.³⁸

POST-TAVI AORTIC REGURGITATION

Post-TAVI AR remains a frequent complication. Moderate or severe paravalvular AR was found in 11.8% of patients at 30 days and 10.5% of patients at 1 year, while moderate or severe transvalvular AR was found in 1.3% at 30 days and 4.2% at 1 year during the PARTNER trial.¹³ Both are associated with raised 30-day and 1-year mortality, and have been identified as an independent predictor of poor postprocedural outcomes.^{16 31} Moderate or severe paravalvular regurgitation is more frequent following a TAVI than in patients undergoing open surgery at both 30 days (12.2% vs 0.9%; $p<0.001$) and at 1 year (6.8% vs 1.9%; $p<0.001$). Interestingly, this occurs despite the finding that transcatheter valve implantation was superior to surgical replacement with respect to both the aortic-valve gradient (10.2 ± 4.3 vs 11.5 ± 5.4 mm Hg; $p=0.008$) and mean valve area (1.59 ± 0.48 vs 1.44 ± 0.47 cm²; $p=0.002$).²¹ The PARTNER trial revealed that at 5-year follow-up there was a significantly increased incidence of moderate or severe AR in the TAVI group compared with the surgical group (14% vs 1%; $p<0.0001$). Once again, the severity of AR was associated with an increased risk of mortality.³⁹

Predictors of post-TAVI AR include undersizing of the valve (due to mismatch of the annulus or prosthesis diameter), aortic route calcification, suboptimal device implantation and the type of valve being implanted. Significant AR is far more common following use of self-expanding CoreValve devices over the balloon expandable Edwards SAPIEN XT, (18.3% vs 4.1%; $p<0.001$) due to increased technical difficulty sizing the valve. As a result, use of the Edwards valve also meant a less frequent need to replace the valve again (0.8% vs 5.8%; $p=0.03$).⁴⁰

Further studies have shown that the incidence of paravalvular leakage is reduced in cases where balloon aortic valvuloplasty has not been used prior to insertion of the prosthetic valve. This novel approach has also been shown to be safe and effective, and along with the development of newer transcatheter heart valve systems, focused on more accurate deployment, repositioning and better sealing of the valve, should lead to a reduction in the incidence of post-TAVI AR.^{29 41–43}

NEED FOR A PERMANENT PACEMAKER FOLLOWING A TAVI PROCEDURE

An important complication of the TAVI procedure is cardiac rhythm disturbance, which can require treatment with a pacemaker in up to 30%–50% of patients.⁴⁴

The pathophysiology behind conduction disturbances is thought to be a combination of pre-existing conduction abnormalities, direct tissue damage occurring during prosthesis deployment, resulting in inflammation and ischaemia and prosthesis characteristics,⁴⁵ for example, Medtronic CoreValve implantation results in a 2.5-fold higher need for a pacemaker than the Edwards SAPIEN valve.⁴⁶

Those with pre-existing conduction abnormalities had an inherent increased risk irrespective of valve type. Those with a baseline first-degree AV block (relative risk (RR): 1.52; $p<0.01$), left anterior hemiblock (RR: 1.62; $p<0.01$) or right bundle

branch block (RR: 2.89; $p < 0.01$) and those with intraprocedural AV block (RR: 3.49; $p < 0.01$) were more likely to need a pacemaker postprocedure.⁴⁶

Due to the close proximity of the aortic valve to the atrioventricular node, unsurprisingly the most common arrhythmia postprocedure is complete heart block, affecting 13.7% of patients and accounting for 68% of the pacemakers that are implanted postprocedure.⁴⁷ Those with a known bundle branch block are far more likely to develop complete heart block postprocedure, with pre-existing right bundle branch block being an independent predictor of complete AV block after TAVI (RR: 7.3, 95% CI 2.4 to 22.2),⁴⁸ due to the left bundle being located close to the aortic root.⁴⁹ Furthermore, pre-existing calcification of the aortic root carries an increased risk of need for a pacemaker, and provides insight into the pathogenesis behind conduction disturbances.⁵⁰

As previously mentioned, NOAF is also a common complication, and in a minority of patients this is slow atrial fibrillation, which requires pacemaker implantation. Other indications for pacemakers include sick sinus syndrome,⁴ and new left bundle branch block, which if persistent carries an independent predictor of all-cause mortality at 1 year (HR 1.84, 95% CI 1.35 to 2.02).⁵¹

Interestingly, the need for a pacemaker is greater following a TAVI than surgical AVR,⁵² and importantly the need for a pacemaker does significantly impact on postprocedure hospital stay and worsens and coexisting heart failure, but does not impact on mortality.⁵³

QUALITY OF LIFE FOLLOWING A TAVI PROCEDURE

Thus far, studies have revealed promising results with regard to survival rates post-TAVI, even in high-risk individuals.⁵⁴ The good survival rates are coupled with a significant increase in quality of life. Within 30 days of the procedure, there was a significantly improved quality of life (baseline 44 ± 19.1 vs 28 ± 17.5 Minnesota living with heart failure questionnaire score, $p < 0.001$) and an enhanced distance in the 6 min walk test (baseline 204 ± 103 vs 266 ± 123 m; $p < 0.001$).⁵⁵

These results are echoed in the elderly, whereby in patients aged over 80 years, the procedure resulted in excellent echocardiographic results, with a significant reduction in the peak aortic valve gradient (before 68.3 ± 21.3 mm Hg; after 10.5 ± 5.6 mm Hg; $p < 0.0001$) and mean aortic valve gradient (before 42.1 ± 14.5 mm Hg; after 4.6 ± 3.2 mm Hg; $p < 0.0001$); and an improvement in both physical component scores (increasing from 28.4 ± 10 to 46.8 ± 9.2 ; $p < 0.001$) and mental component scores 7.3 ± 10.8 to 50.6 ± 10.1 ($p < 0.001$) with the greatest improvement being seen in physical functioning (190% increase).⁵⁶

These survey results were reflected in an improvement in average New York Heart Association (NYHA) class in patients from baseline to 6 months after valve implantation (NYHA baseline 3.1 ± 0.6 vs after 1.4 ± 0.6 ; $p < 0.0001$), along with a reduction in serum NT-proBNP ($9299 \pm 10\,658$ vs 2075 ± 2776 ng/L; $p < 0.05$),⁵⁰ which is an established marker of quality of life and outcomes in patients with heart failure.⁵⁷

A large multicentre trial comparing health status in patients who underwent a TAVI with those who underwent surgical AVR, demonstrated 1 month following the procedure, those who underwent TAVI showed a significant improvement in symptoms, physical function and quality of life. However, by 6 months these differences were no longer apparent. Interestingly, the observed differences were only present in those who underwent TAVI via iliofemoral access. In those

undergoing TAVI via non-iliofemoral access (performed either via subclavian artery or direct aortic approach), there was no significant difference when compared with open surgery. This may be because the ministernotomy required during the direct aortic approach impacts on recovery; therefore, those treated via the iliofemoral route experienced more rapid improvements.⁵⁸

Following TAVI, the previously increased myocardial stress caused by aortic stenosis returns to normal, and this is reflected in the neurohormonal activity, quality of life and functional capacity of patients. The procedure has a beneficial impact on mortality and also on desired measures of quality of life, with the most rapid improvements being seen when the iliofemoral route is used.

LIMITATIONS

In spite of greater operator experience and improvements in TAVI technology, patients treated with this revolutionary procedure remain a high-risk, fragile patient group. The contemporary TAVI devices have certain limitations that should be considered and potential solutions should be provided.

Vascular complications

Vascular complications occur in up to 25% of all patients undergoing TAVI, and major events are associated with adverse clinical outcomes. Small vessel dimensions, moderate or severe calcification and tortuosity of the peripheral vasculature are associated with an increased incidence of complications. As a result, novel endovascular techniques may allow non-invasive management of arterial complications and newer devices have been developed to enable delivery through lower profile sheaths to further reduce vascular complications.⁵⁹

Acute kidney injury

It has common occurrence following TAVI (and when severe it is an independent predictor of adverse outcomes), as a consequence of numerous factors including underlying chronic kidney disease, contrast-induced nephropathy and peripheral embolisation. New strategies have recently evolved, including the RenalGuard system (RenalGuard Solutions, Milford, Massachusetts, USA), which may have a potential role.⁶⁰

Stroke

The incidence of clinical stroke following TAVI is approximately 3%–4%, although numerous imaging studies have demonstrated higher occurrence of new cerebral ischaemic defects in a larger proportion of patients with unclear clinical significance. Anatomical features such as the presence of a severely stenotic and calcified aortic valve, use of large delivery systems and multiple manipulations during device implantation have been associated with an increased risk of stroke. Furthermore, new onset of atrial arrhythmias (which are noted in up to one-third of patients undergoing TAVI) may also be important.⁶¹

A number of strategies are under investigation to reduce stroke, including aggressive anticoagulant and antiplatelet strategies and the use of dedicated cerebral protection devices (eg, Claret dual-filter cerebral protection system (Claret Medical, Santa Rosa, California, USA) and Embrella device (Edwards LifeSciences)). Use of these devices has been shown to significantly reduce the number of ischaemic cerebral lesions in the protected brain regions, but follow-up in larger numbers of patients is required to demonstrate efficacy.

NEW GENERATION OF VALVES FOR TAVI

Despite growing experience, issues remain associated with first-generation TAVI devices (Edwards SAPIEN XT, Medtronic CoreValve) including valve malpositioning, vascular complications, paravalvular regurgitation and conduction disorders. The ideal TAVI system is repositionable and fully retrievable, results to no paravalvular leak, has reproducible depth to cause less rhythm issues, is easy to use and has low-risk profile from the point of both the valve and the sheath.^{62 63}

Several second-generation TAVI devices (Edwards SAPIEN 3, Medtronic Evolut R, Boston Scientific Lotus, Direct Flow Medical), aimed at sorting out these issues, are CE marked or under evaluation for CE marking. We address the results of a single-centre study⁶⁴ that took place between November 2007 and May 2015, with a total of 449 patients treated with 1G TAVI devices who were propensity matched (1:1) to 179 patients treated with 2G TAVI devices. The primary end point was 30-day safety according to the Valve Academic Research Consortium 2 definition. According to the results, patients treated with 1G devices suffered more adverse events at 30-day

follow-up (freedom of adverse events, 75.3% vs 88.8%; HR, 2.4; 95% CI 1.4 to 4.0; $p=0.01$) and a significantly greater number of minor vascular complications (31.8% vs 10.4%; $p<0.001$) and major vascular complications (3.2% vs 0.6%; $p<0.001$) compared with patients treated with 2G devices. The presence of residual AR ≥ 2 was also greater in the 1G group (17.5% vs 5.8%). There were no differences between groups with regard to 30-day all-cause mortality (5.2% vs 3.2%; OR, 0.61 and $p=0.40$).

Current data suggest that contemporary 2G devices are associated with a significant safety benefit at 30 days and reduction of residual moderate or severe paravalvular leak. Long-term follow-up in more patients is required to determine if these short-term benefits translate into improvements in long-term clinical outcomes (table 1).^{65–76}

PROSPECTS OF CLINICAL APPLICATION OF TAVI

The application of TAVI to intermediate-risk patients were recently assessed in a randomised trial at 57 centres and with 2032 patients who had either TAVI or surgical AVR, with

Table 1 Studies involving new generations of TAVI valves

Device name and valve size	Valve structure	Delivery system and access route	Clinical evaluation studies
JenaValve (23, 25 and 27 mm for 21–27 mm aortic annuli)	Porcine pericardial tissue valve, self-expanding nitinol stent	Sheathless 32 FrTransapical (transfemoral is under clinical evaluation)	JUPITER registry ⁶⁵ (180 patients): 85% overall survival (30 days), 12.5% pacemaker implantation, no major strokes, 1.3% acute MI (30 days), 97.6% mild or absent perivalvular leakage
ACURATE (small 20–23 mm, medium 23–25 mm and large 25–27 mm aortic annuli)	Porcine pericardial tissue valve, self-expanding nitinol alloy stent	Sheathless 28 FrTransapical (transfemoral is under clinical evaluation)	ACURATE TA ⁶⁶ (40 patients): 92.5% device success rate, 82.5% survival (6 months), 7.5% pacemaker implantation, 97.5% small perivalvular leakage ACURATE TF ⁶⁷ (20 patients): 95.6% procedural success, 13% pacemaker implantation, 95% mild or absent perivalvular leakage
Portico SJM (23 and 25 mm)	Bovine pericardial tissue valve, self-expanding, nitinol frame, porcine pericardial cuff	Transfemoral, transaortic or subclavian: 18 Fr Transapical: sheathless 24 Fr (currently only transfemoral approved)	Multicenter clinical study ⁶⁸ (102 patients): 30-day mortality, disabling stroke and major vascular complications were 2.9%, 2.9% and 5.9%, respectively. Resheathing and repositioning (23.8%) was successful in all instances, 9.8% pacemaker implantation
Direct Flow Medical (25 and 27 mm)	Bovine pericardial tissue valve, two polyester rings filled with polymer solution	Transfemoral, 18 Fr outer diameter	DISCOVER trial ⁶⁹ (75 patients): 99% overall survival (30 days), 2.7% major strokes, 4% life-threatening bleeding, 16% pacemaker implantation, 99% mild or absent perivalvular leakage (30 days)
Engager Medtronic (23 and 26 mm for 21–26.5 mm aortic annuli)	Bovine pericardial tissue valve, self-expanding, nitinol frame and a polyester skirt	Transapical, transaortic access 29 Fr inner diameter	Engager European pivotal trial ⁷⁰ (61 patients): all-cause mortality was 9.9% at 30 days and 16.9% at 6 months, no paravalvular regurgitation greater than mild through 6 months, implantation success and valve safety
CoreValve Evolut Medtronic (23 mm)	Porcine pericardial tissue valve, self-expanding nitinol frame	Transfemoral, transaortic and subclavian: AccuTrak stability layer (18 Fr outer diameter)	Valve-in-valve study ⁷¹ (126 patients): 100% procedural success rate, no deaths or adverse events related to the procedure or device (30 days), 0% pacemaker implantation
Lotus valve Boston Scientific 23 and 27 mm	Bovine pericardial tissue valve, self-expanding, braided nitinol frame	Transfemoral 18 Fr, minimum vascular access diameter 6.0 mm (23 mm valve) or 6.5 mm (27 mm valve)	REPRISE II trial ⁷² (120 patients): at 1 year 88.6% patients had no or trivial paravalvular aortic regurgitation, all-cause mortality rate 10.9%, disabling stroke rate 3.4%, disabling bleeding rate 5.9%, with no repeat procedures for valve-related dysfunction and 31.9% pacemaker implantation
Edwards SAPIEN 3 26 mm (20, 23 and 29 mm sizes anticipated)	Bovine pericardial tissue valve, balloon expandable cobalt chromium frame	Transfemoral (transapical and transaortic under clinical evaluation) Edwards sheath 14 Fr with dynamic expansion mechanism	SAPIEN 3 study ⁷³ (15 patients): 100% procedural success rate, 6.7% pacemaker implantation, no deaths/strokes/cardiovascular complications, 100% mild or absent perivalvular leakage (30 days)
Edwards CENTERA 23, 26 and 29 mm	Bovine pericardial tissue valve, self-expanding nitinol frame with polyethylene terephthalate skirt	Transfemoral and subclavian access, Edwards sheath 14 Fr with dynamic mechanism and motorised handle	First device (15 patients): 100% procedural success rate, 27% pacemaker implantation, 92% mild or absent perivalvular leakage (30 days) ⁷⁴ New configuration device (14 patients): 100% procedural success rate, 0% pacemaker implantation, 100% mild or absent perivalvular leakage ⁷⁵
Helio Edwards 25 mm	Self-expanding nitinol stent encased in polyethylene terephthalate	Transfemoral Edwards sheath 16 Fr	Helio feasibility trial ⁷⁶ (4 patients): 100% implantation success, 100% freedom from all-cause mortality (30 days), 2 patients reached 12-month follow-up with no residual aortic regurgitation

TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.

primary end points being death from any cause or disabling stroke at 2 years. The rate of death from any cause or disabling stroke was similar in the TAVI group and the surgery group ($p=0.001$ for non-inferiority). At 2 years, the Kaplan-Meier event rates were 19.3% in the TAVI group and 21.1% in the surgery group (HR in the TAVI group, 0.89; 95% CI 0.73 to 1.09; $p=0.25$). TAVI resulted in larger aortic valve areas than did surgery and also resulted in lower rates of acute kidney injury, severe bleeding and new-onset atrial fibrillation, but surgery resulted in fewer major vascular complications and less paravalvular AR.⁷⁷

Multicenter studies were previously held to assess application of TAVI to patients with severe stenosis of bicuspid aortic valve, and the outcomes seem generally encouraging but certain limitations should be noted. Although these studies suggest feasibility of TAVI in patients with bicuspid aortic valve, and are encouraging particularly in regard to AR, there are a few concerning signals: higher-than-typical rate for new pacemakers and frequent asymmetric valve expansion with an unknown effect on long-term prosthesis durability. Further progress is expected with the next-generation valves and more data are needed on the subtypes of bicuspid aortic stenosis and the long-term outcomes of this approach before this therapy can become standard for these patients.^{78 79}

CONCLUSION

Calcific aortic valve stenosis is a common valvular abnormality, and without corrective surgery it carries a high morbidity and mortality. TAVI is a novel and effective procedure, in which a bioprosthetic valve is implanted within the severely stenotic native aortic valve. It is a new therapeutic modality for treatment of older patients with severe symptomatic aortic stenosis and other comorbidities, who have inherently a high surgical risk. Embolic strokes, however, remain a troublesome adverse event following TAVI and careful patient selection appears crucial to maintain good outcome.

With increasing technical expertise, continuing reduction of the complication rates and improving technological advances and delivery systems, the use of this technique to treat patients with severe aortic stenosis but without significant comorbidity, who now undergo open-heart surgery, may become possible in the future. The integration of this procedure in routine clinical practice is likely to lead to further discussions between the main parties including the patients, health care providers and commissioning groups, clinicians, regulatory agencies, industry and professional societies.

Main messages

- ▶ The transcatheter aortic valve implantation (TAVI) procedure has revolutionised the treatment of aortic stenosis, especially for those patients previously deemed as too high risk to undergo valve replacement.
- ▶ Its success is evident in the reduced morbidity and mortality rates and increase in quality of life postprocedure.
- ▶ Success rates are likely to improve even further with the introduction of second-generation valves, which aim to be repositionable and fully retrievable.

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Current research questions

- ▶ Describe how the transcatheter aortic valve implantation (TAVI) procedure is carried out and the benefits of the various approaches that can be used?
- ▶ Describe the benefits of TAVI over both balloon aortic valvuloplasty and open-heart surgery?
- ▶ Describe the various types of second-generation valves and the advantages they have over first-generation valves?

Self assessment questions

Please answer true or false to the below statements.

1. Currently, the transcatheter aortic valve implantation (TAVI) procedure is being used to replace stenotic bicuspid aortic valves.
2. The development of new-onset atrial fibrillation (NOAF) following a TAVI procedure is a poor prognostic indicator.
3. Edwards SAPEIN valve implantation results in a greater need for postprocedure permanent pacemaker implantation than Medtronic CoreValve implantation.
4. Following a TAVI procedure, patients with heart failure have a reduction in their New York Heart Association (NYHA) class, but not in serum N-terminal probrain natriuretic peptide.
5. The development of second-generation TAVI devices has led to a reduction in adverse events, including both minor and major vascular events.

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Answers

1. False
2. True
3. False
4. False
5. True