Heart Online First, published on January 2, 2015 as 10.1136/heartjnl-2014-306254

Transcatheter aortic valve replacement: current perspectives and future implications

Shikhar Agarwal, E Murat Tuzcu, Amar Krishnaswamy, Paul Schoenhagen, William J Stewart, Lars G Svensson, Samir R Kapadia

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2014-306254).

Sones Cardiac Catheterization Laboratories, Department of Cardiovascular Medicine, J2-3, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to
Dr Samir R Kapadia, Sones Cardiac Catheterization Laboratories, Department of Cardiovascular Medicine, J2-3, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA; kapadis@ccf.org

Received 8 September 2014
Revised 26 October 2014
Accepted 27 October 2014

ABSTRACT

Transcatheter aortic valve replacement (TAVR) or transcatheter aortic valve implantation (TAVI) has emerged as an attractive treatment strategy for the treatment of patients with severe symptomatic aortic stenosis (AS), particularly those who are inoperable or at high risk for surgical aortic valve replacement. Several multicentre registries and randomised trials have demonstrated the safety and efficacy of this technology in improving the survival as well as functional capacity of patients with AS. Most of the elderly patients with severe AS have multiple non-cardiac comorbidities, which might limit survival and impede the improvement in functional capacity afforded by TAVR. Therefore, optimal patient selection based on precise risk assessment is currently the cornerstone of evaluation of patients for TAVR. Due to the need for a multifaceted approach in patient evaluation, procedural conduct as well as postprocedure management, multidisciplinary heart valve teams have assumed a paramount role in the TAVR process. This review presents the current perspectives in patient selection, risk assessment, procedural considerations and outcomes following TAVR, along with implications for the future.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) or transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement (SAVR) for the treatment of patients with severe symptomatic aortic stenosis (AS), especially among the inoperable or high-risk patients.[1 2] Since the first TAVR performed by Alan Cribier in 2002, over 100 000 procedures have been performed to date across the world with either a balloon-expandable valve (BEV) (Edwards SAPIEN valve) or the self-expanding valve (SEV) (Medtronic CoreValve). The safety and effectiveness of the SAPIEN valve and the CoreValve have been thoroughly and convincingly established through well-designed randomised control trials (RCT), namely the Placement of Aortic Transcatheter Valves (PARTNER) trial and the US CoreValve pivotal trials.[1–3] Although most of our extensive experience stems from these two valves, several additional valves are currently in development and several others are undergoing clinical testing. With further growth and development of this transformative technology, the treating physicians will be faced with the difficult task of making determinations about patient selection and the choice of valve, access routes and methods to mitigate postprocedural complications.

To cite: Agarwal S, Tuzcu EM, Krishnaswamy A, *et al*. *Heart* Published Online First: [*please include* Day Month Year] doi:10.1136/heartjnl-2014-306254

PATIENT SELECTION

Optimal patient selection is the cornerstone of a successful TAVR programme. A global sharing of information, training and experience over the past decade has led to a significant improvement in the overall patient selection process, which has likely contributed to an improvement in the outcomes. One of the key requirements of a successful TAVR programme is a multidisciplinary heart team that includes interventional cardiologists, cardiac surgeons, imaging specialists, anaesthesiologists, nurse coordinators, as well as other clinical and research staff, all of whom perform in a complimentary fashion with a clear understanding of their role in the team. The responsibilities of the team members include case screening, deciding the optimal treatment strategy, planning the procedure details, as well as detailing the postprocedure management including postdischarge care. Figure 1 demonstrates the workflow process involved in a typical TAVR programme aided by a heart valve team. Patient selection, by far, is one of the most important responsibilities of the multidisciplinary heart valve team.

Anatomical considerations are generally evaluated first to rule out any obvious contraindications. All patients presenting for TAVR evaluation are subjected to extensive imaging including transthoracic echocardiography (TTE), multidetector CT (MDCT) and angiography. Other modalities such as transoesophageal echocardiography (TEE) or magnetic resonance imaging (MRI) may be used when further imaging is needed. An important preliminary assessment includes the evaluation of size, tortuosity and degree of calcification of the iliofemoral arteries. Most heart teams use MDCT; others use angiography to determine the feasibility of the transfemoral (TF) approach (see online supplementary figure S1). The size of the aortic annulus is assessed using a 3D imaging modality (figure 2). MDCT is used widely for this purpose. Some groups may prefer 3D-TEE or MRI, particularly to avoid radio-contrast agents in patients with renal insufficiency. Aortic root angiography is used as adjunctive imaging in some patients such as those who require TAVR for the treatment of failed surgical prosthesis.

In the absence of a well-validated dedicated TAVR risk score, the risk assessment is currently guided by calculation of either the logistic EuroSCORE (LES) or the Society of Thoracic Surgeons (STS) score.[4 5] Although applied routinely to the TAVR populations, these scores were not developed for high-risk patients with severe AS. Conditions that may pose prohibitive surgical risk from the technical standpoint include radiation heart disease, heavily calcified or porcelain ascending aorta and multiple prior chest surgeries

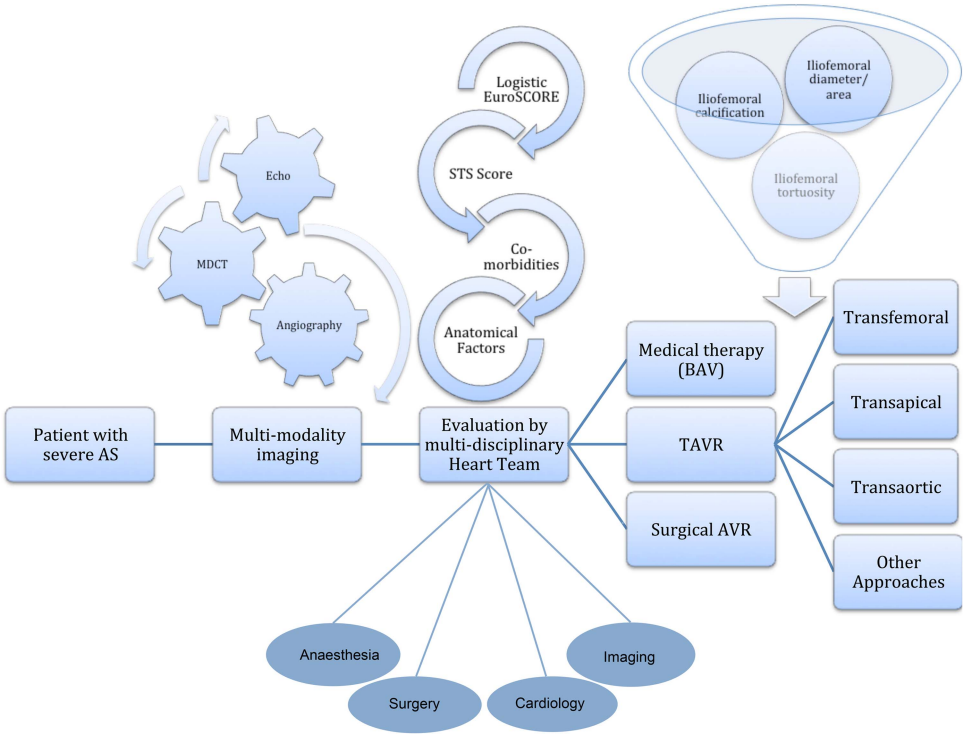

Figure 1 Workflow process involved in the evaluation and management of a patient presenting with severe symptomatic AS. The figure illustrates the importance of multimodality imaging and the central role of the multidisciplinary heart team in the evaluation of these patients. AS, aortic stenosis; AVR, aortic valve replacement; BAV, balloon aortic valvuloplasty; MDCT, multidetector CT; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

with adhesions, prior sternal wound infection or bypass graft anatomy such as left internal mammary graft adhered anteriorly under the sternum. In addition to these, profound LV dysfunction, small (<18 mm) or large (>27 mm) aortic annulus, intracardiac mass, thrombus or vegetation and location of the left main coronary ostium within 10 mm of the annulus with large bulky aortic valve leaflets, severe pulmonary hypertension may serve as impediments against successful TAVR. Several of these characteristics are not included in the STS score or LES, making these scores possess poor discriminatory ability for adverse outcomes following TAVR.

Coronary angiography is routinely performed during TAVR evaluation. Significant coronary artery disease (CAD) is commonly encountered in 40%–75% of patients with severe AS being evaluated for TAVR.[6] The impact of CAD on short-term and long-term outcome after TAVR and their optimal management is not clear at the time of this writing. As the field of TAVR has evolved, it has become apparent that even in the presence of CAD, unless the stenoses are very severe and compromise large areas of myocardium, TAVR can be performed safely. However, the long-term impact of an unrevascularised state is unknown. When needed, percutaneous coronary intervention (PCI) can be safely performed in patients with severe AS without an increased risk of short-term adverse outcomes, particularly in those with preserved LV function. If PCI is needed, the optimal timing is also an area of differing opinions. The potential advantages of revascularisation prior to TAVR include a simplified access to the coronaries before TAVR and a lower risk of ischaemia and haemodynamic instability during rapid pacing and balloon inflation during subsequent TAVR. The choice of stent for PCI should be individualised based on comorbidities, bleeding risk factors and ability to take dual antiplatelet therapy.

Although not studied in RCT settings, accumulated experience suggests that several patient groups would benefit from TAVR rather than SAVR. These include patients with radiation heart disease, particularly those who need reoperation, advanced chronic kidney disease, advanced chronic liver disease, degenerated surgical bioprosthetic valves, low-gradient AS or those with treatable malignancies or conditions that require treatment of severe AS prior to undergoing definitive treatment of the underlying condition. Several of these patient groups are unlikely to be ever studied in the context of a randomised trial. Although most of the current TAVR experience is limited to severe AS affecting a trileaflet valve, some anatomical 'off-shoots' are already available in the current literature. Although bicuspid aortic valve anatomy has been considered a relative contraindication for TAVR, several studies have reported on the technical feasibility in this anatomic setting.[7] A recent systematic review on the procedural outcomes following TAVR in bicuspid aortic valve patients demonstrated 30-day mortality rate of 8.6%.[7] The incidence of significant paravalvular aortic regurgitation (PAR) (moderate or more) was noted to be 31%, which was significantly higher than that encountered in the PARTNER trial.[7] Although the data are still limited, TAVR has been shown in small number of cases to be feasible and effective in appropriately selected cases of pure aortic regurgitation in native aortic valves.[8]

Besides these indications, TAVR has been demonstrated to be technically feasible in cases of failed surgical bioprostheses.[9] Preliminary data from the Valve-in-Valve International Data registry reported a high procedural success rate (93.1%) with low incidence of short-term mortality (7.6% at 30 days) and major stroke (1.7% at 30 days).[9] The overall 1-year mortality rate was 83.2%.[9] Survival was found to be lower among patients with small surgical bioprosthesis (≤21 mm) and predominant valve stenosis (vs regurgitation).[9]

Low-gradient severe AS has been associated with significant mortality after SAVR, approaching 35% especially in patients with no contractile reserve.[10] TAVR is feasible in patients with severe comorbidities and low-flow, low-gradient AS.[11] Although

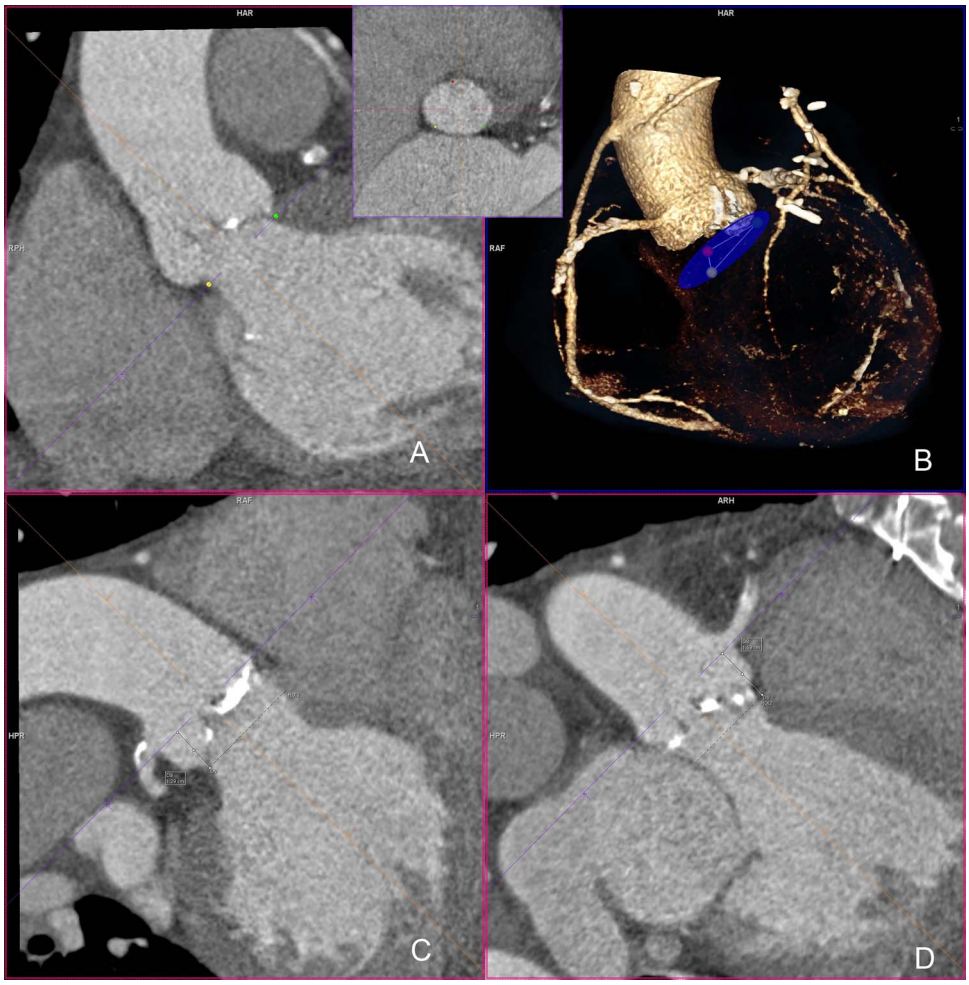

Figure 2 Multidetector CT of the aortic annulus and the aortic root. (A) The aortic root in projection, orthogonal to the annular plane. (B) The volume rendered image of the aortic root showing the valve annular plane. The inset between (A) and (B) shows the annulus reconstruction that is used to make measurements. (C) The measurement of the distance between the annular plane and the left main trunk. (D) The measurement of distance between the annular plane and the right coronary artery.

short-term mortality may be considerably high in this cohort, the surviving patients showed symptomatic benefit and significant improvement of myocardial function and exercise capacity along with significant improvement in quality of life.[11] In addition, feasibility and safety of TAVR has been demonstrated in low-flow, low-gradient, severe AS in both preserved and reduced EF, with 1-year mortality rates comparable with high-gradient severe AS.[12]

RISK ASSESSMENT

Owing to the advanced age of patients, important comorbidities and life expectancy must be assessed prior to embarking on the choice of therapy. TAVR should not be offered to patients who have non-cardiac illnesses that are the predominant cause of the limiting symptoms or to those who have an estimated life expectancy <12 months from non-cardiac illnesses. The benefits of TAVR in elderly, high-risk patients must be viewed beyond the crude mortality metrics and should certainly incorporate the value of early recovery and quality-of-life measures. It has been suggested that the optimal definition of 'poor outcome' after TAVR should reflect a failure to achieve the goals of intervention, and hence should incorporate a quality-of-life component in addition to mortality.[13 14] Based on this conceptual framework using data from the PARTNER trial, Arnold *et al*[13 14] have suggested the most appropriate definition of 'poor outcome' at 6 months following TAVR is death or Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score <45 or ≥10-point decrease in the KCCQ-OS score compared with the baseline. Using this definition, the authors demonstrated that the most important predictors of poor outcomes were poor functional capacity (as measured by the 6 -minute walk test) and lower mean aortic valve gradients.[13 14] Other important predictors included oxygen-dependent lung disease, renal dysfunction and poorer baseline cognitive function.[13 14] Risk-assessment algorithms like these that incorporate hard clinical endpoints along with quality-of-life measures are likely to become instrumental in the assessment of patients referred for TAVR. It is of critical importance to reliably identify patients who are unlikely to benefit in terms of survival or functional capacity following TAVR.

Therapeutic futility has been defined as the lack of efficacy from a medical treatment. It includes both lack of intended clinical benefit, as judged by a physician and lack of meaningful survival and improvement in functional capacity, as judged by a patient. Assessment of futility, therefore, is a collective decision based on physician impressions as well as personal values and preferences of the patient. Shared decision making is vital to the evaluation process, wherein both the patient and the physician share information, work towards a common understanding and reach an agreement on the therapeutic strategy. Lindman *et al*[15]

have recently proposed a framework for assessment of patients presenting for TAVR evaluation (figure 3). This includes clinical risk stratification, geriatric risk stratification, anticipated benefit of TAVR and patient preferences. Beyond these traditional clinical comorbidities, there are several age-related conditions that may predispose an elderly patient to adverse outcomes following TAVR. These include frailty, disability in activities of daily living, malnutrition, mobility impairment, low muscle mass (sarcopenia), cognitive impairment, mood disorders and social isolation. Incorporation of measures of frailty has demonstrated an improvement in risk stratification prior to TAVR.[16]

PROCEDURAL CONSIDERATIONS

Procedural suite

In most referral centres, TAVR is performed in a hybrid procedure suite, which fulfils the requirements of a cardiac catheterisation laboratory and an operating room. It should be equipped with high-resolution fluoroscopy and haemodynamic monitoring systems necessary for a cardiac catheterisation laboratory, along with the infrastructure of a surgical suite, including cardiopulmonary bypass, mechanical ventilation and surgical paraphernalia. In the USA, the presence of an interdisciplinary team, comprising interventional cardiologist, cardiothoracic surgeon, cardiac anaesthesiologist, perfusionists and ancillary staff, during the procedure is necessary. Availability of the cardiac surgeon during the TAVR procedure is an important asset and may be the determining factor in the setting of a rare but life-threatening complication such as ventricular perforation, annulus rupture, coronary obstruction, acute mitral insufficiency and device embolisation. Availability of advanced imaging technologies like 3D TEE, Dyna CT C-arm, C-THV (Paieon, New York, New York, USA), HeartNavigator (Philips Healthcare, Andover, Massachusetts, USA) and ValveAssist (GE Healthcare) to facilitate real-time 3D visualisation of the vascular structures, and better assessment of the aortic annulus anatomy has been used by some groups (figure 4).[17] Because many of the procedures conducted in hybrid suites are at the forefront of the field, they often carry a high degree of procedural risk. It is, therefore, important that the hybrid suite contain ready-made 'crash carts' consisting of any equipment necessary in case of an emergency. For instance, our hybrid suite has one cart containing all of the tools necessary to initiate emergent cardiopulmonary bypass and another cart for emergent peripheral endovascular intervention. There is often little time to spare in these situations, and since solutions often require novel uses of existing equipment it is important to plan accordingly to minimise both physical and mental time necessary to act rapidly.

As the experience with TAVR has increased, some centres have started performing TF-TAVR in a standard catheterisation laboratory without general anaesthesia or TEE guidance.[18] It has been recently demonstrated that TF-TAVR performed using a 'minimalist approach' (local anaesthesia, conscious sedation, fully percutaneous access site entry and closure and TTE) can be performed safely and effectively. The shorter length of stay along with lower resource use with the 'minimalist approach' reduces hospital costs and might facilitate the logistics of TF-TAVR.

Valve selection

Although there are a number of approved transcatheter valves available for clinical use in Europe, there are only two approved valves in the USA. The valves manufactured by Edwards Lifesciences are BEV made of bovine pericardium mounted in a short cylindrical stent. The valves manufactured by Medtronic are SEV made of porcine pericardium mounted in a taller nitinol stent with an adaptive shape. Currently, both these valves are US Food and Drug Administration-approved for use in patients, who are at extreme or high risk for surgical AVR due to comorbidities or anatomical considerations. There is a paucity of data surrounding comparison of different valve types. The Comparison of Transcatheter Heart Valves in High-Risk Patients with Severe Aortic Stenosis: Medtronic CoreValve vs Edwards SAPIEN XT (CHOICE) trial is the first and the only RCT that has attempted to compare procedural and short-term outcomes following implantation of SEV versus BEV.[19] The CHOICE trial demonstrated a significantly higher rate of 'device success' with BEV than SEV.[19] In addition, the trial demonstrated a significantly higher incidence of residual PAR following SEV implantation compared with the BEV implantation. Although the trial shed some light on differences in procedural as well as short-term outcomes between the two valve types, the intermediate or long-term comparative outcomes are not yet available. In addition, the CHOICE trial had limitations of a small patient cohort and lack of a core laboratory for adjudicating echocardiographic outcomes.

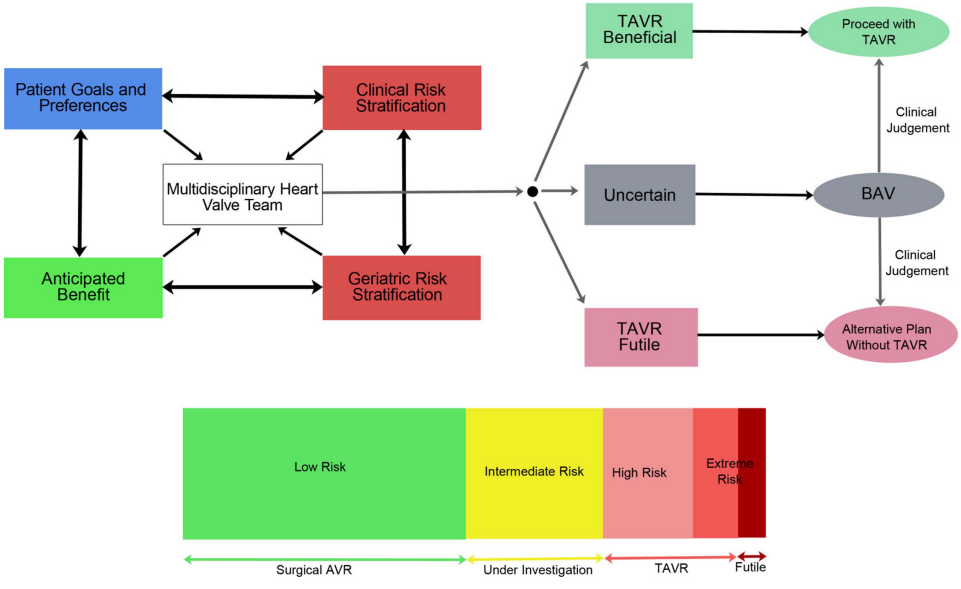

Figure 3 Decision making by the multidisciplinary heart team on patients referred for TAVR. The multidisciplinary team considers and weighs the various risk factors shown and makes a decision regarding whether TAVR would be beneficial or futile (adapted from Lindman *et al* [15]). AVR, aortic valve replacement; BAV, balloon aortic valvuloplasty; TAVR, transcatheter aortic valve replacement.

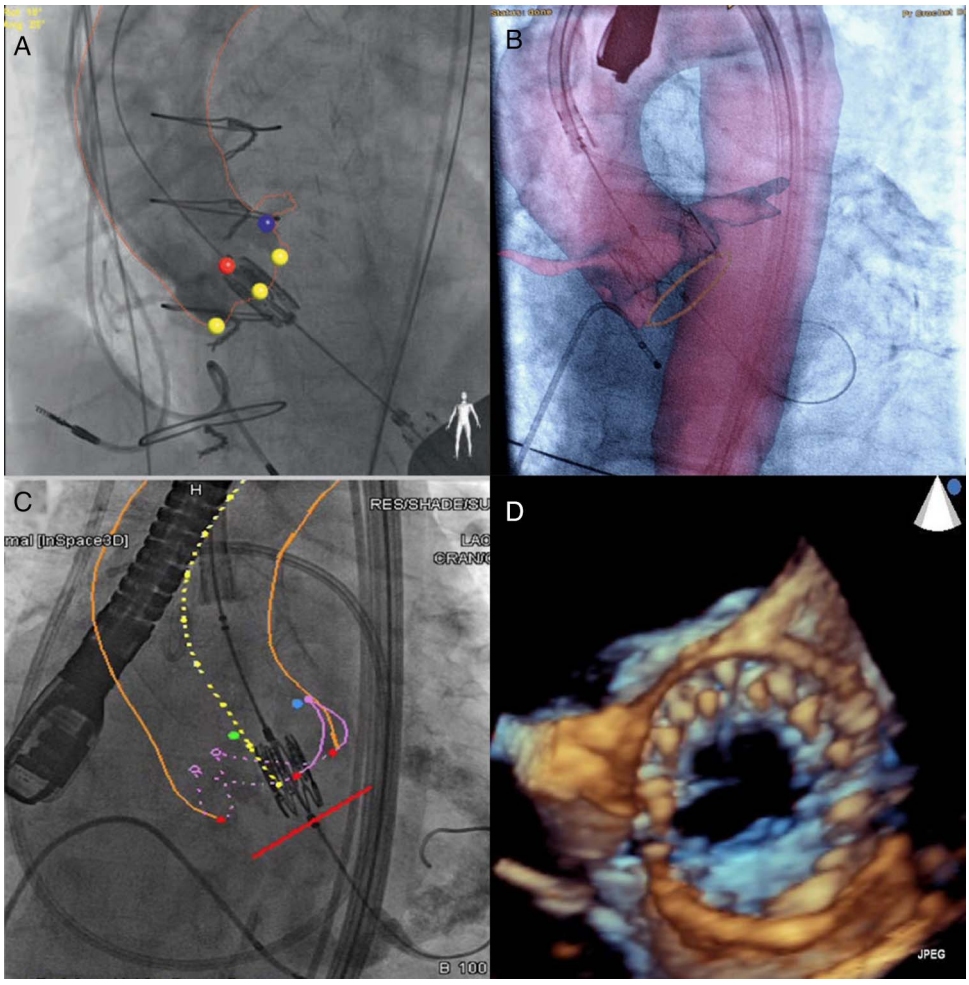

Figure 4 Use of new technology for performing transcatheter aortic valve replacement (TAVR). (A) Philips HeartNavigator overlay during final positioning of the transcatheter valve. (B) The use of GE Healthcare ValveAssist, which enables facilitating TAVR by integrating computed tomographic data on live fluoroscopic imaging. (C) Fluoroscopic overlay of an outline of the aortic root during valve positioning using DynaCT. Automated analysis provides marking of the annulus at the nadir of each sinus (red dots), left coronary ostium (blue dot) and right coronary ostium (green dot). The red line demonstrates the perpendicular C-arm angulation; if a circle is seen, the angle is not perpendicular to the annulus. (D) A deployed Edwards SAPIEN valve in the optimum position using 3D transoesophageal echocardiography.

With the increasing availability of several different valves to choose from, the cardiologists would need to adopt an 'anatomy-dependent' valve selection process to treat each patient with the perfectly fitting valve. For example, patients with heavy annulus calcification, annulus eccentricity and aorta-LV outflow tract (LVOT) angle are more predisposed to have residual PAR after SEV implantation[20 21] and may be more suitable for BEV implantation. Conversely, if the coronary ostia are very low and close to the annulus, SEV may be preferable to BEV.[22] However, it should be noted that local expertise has to be considered before selecting the valve type since operator experience is one of the most important factors in ultimate success. It would be desirable that centres performing TAVR have access and expertise to use both devices as they have complementary characteristics.

Access selection

The TF access serves as the default route for valve implantation among patients with suitable iliofemoral anatomy (figure 5). Evaluation of the size, tortuosity and the degree of calcification of the iliofemoral arteries using MDCT or angiography is mandatory to determine the feasibility of TF approach (see online supplementary figure S1). The Edwards SAPIEN valve can be implanted retrogradely via the TF or the transaortic approach as well as in an antegrade fashion by transapical approach. The CoreValve can be implanted via TF, transaortic and trans-subclavian approaches. Among patients with unsuitable iliofemoral anatomy, an alternative access route may need to be used. Typically, a trans-subclavian access route is used for CoreValve implantation for patients with unsuitable iliofemoral anatomy. The most common alternative access route for the Edwards valve is the transapical route, wherein the valve prosthesis is delivered in an antegrade fashion through the LV apex (see online supplementary figure S2). Despite the availability of these approaches, there remains a considerable number of patients who are not candidates for either approach because of poor vascular access, poor pulmonary function or chest pathology. Among these patients, the valve prosthesis may be delivered using a retrograde approach by direct cannulation of the ascending aorta or the carotid artery or the subclavian artery (see online supplementary figures S2 and S3). More recently, caval-aortic access has been described for TAVR, wherein percutaneous entry is obtained into the abdominal aorta from the femoral vein through the adjoining inferior vena cava. Rarely these days TAVR has been performed through the trans-septal route in the absence of suitable iliofemoral access similar to the

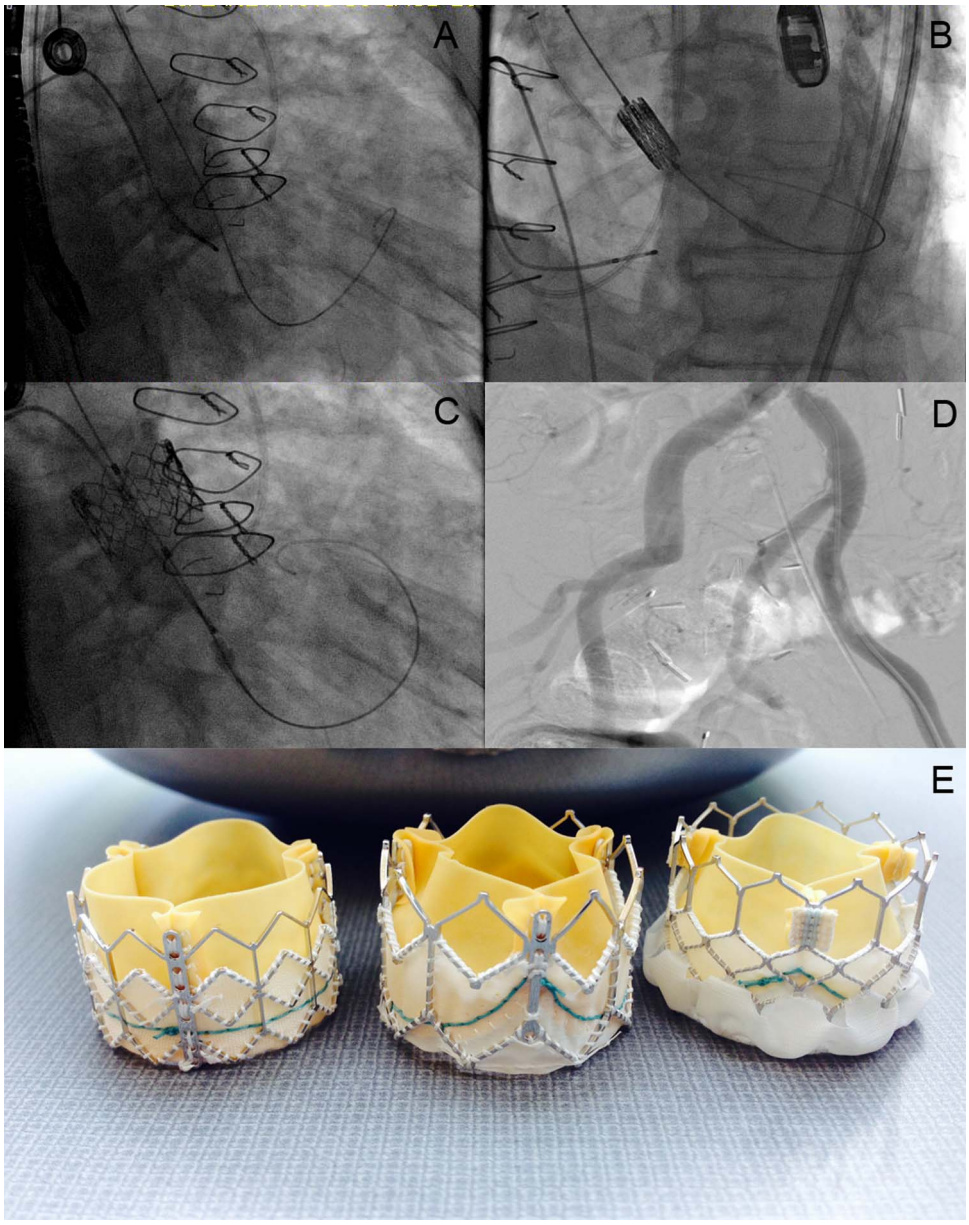

Figure 5 Transfemoral placement of the Edwards SAPIEN aortic valve prosthesis. (A) The balloon aortic valvuloplasty prior to valve placement. (B) The positioning of the valve prosthesis. (C) The deployed valve in optimal position. (D) Angiography of the right femoral artery from the contralateral side, after vascular closure to ensure the absence of major vascular complications. (E) The three generations of the Edwards SAPIEN valves.

initial reports by Dr Cribier (see online supplementary figure S4).

With the use of newer-generation lower profile valves and a reduction in the size of delivery sheaths, a significantly larger proportion of patients are undergoing TAVR through femoral access. A comparison of outcomes between TF and alternative access is confounded by a significant difference in the baseline characteristics of the two cohorts. Data from the PARTNER continued access registry have shown that the results obtained from the transapical implantation were similar to those from TF implantation of Edwards valves. However, results from the German Aortic Valve Registry have demonstrated better outcomes following TF TAVR compared with transapical TAVR.[23] In the modern era, most TAVR centres follow a clear 'transfemoral first strategy', which leads to higher-risk patients getting selected for alternative access, contributing to a significant selection bias in this comparison.

PROCEDURAL OUTCOMES

Over the last decade, TAVR has been immensely successful in reducing short-term as well as medium-term mortality among patients with severe AS. Table 1 demonstrates the incidence of mortality and stroke across seminal multicentre registries and RCTs.

Mortality

We have demonstrated earlier that the pooled 30-day mortality in RCTs is significantly lower compared with the pooled mortality obtained from multicentre registries.[24] This is likely due to multiple factors including rigorous pre-procedural assessment, exclusion of patients with advanced comorbidities and an extensive procedural planning in the RCTs. The trial sites included the best valve centres with extensive surgical experience and support with good infrastructure for the procedure. Despite these short-term differences in 30-day mortality rates, the

1-year all-cause mortality rates are similar in the multicentre registries and RCTs.[24] This point highlights the fact that procedural mortality is important, but the patient selection is probably more important in these patients because there is a considerable risk of mortality in the first year even after a successful procedure. A significantly large proportion of all-cause deaths at 1 and 2 years are attributable to non-cardiovascular causes. In the future, it would be crucial to identify the patient population that is likely to derive the most benefit from the TAVR technology in the perspective of cost-effectiveness.

Stroke

Despite a decline in the incidence of stroke in recent years, it remains an important cause of morbidity and mortality following TAVR. Manipulation of the aortic arch and the aortic root during valve implantation has been implicated as a mechanism for stroke in the immediate periprocedural period. Majority of the strokes following TAVR occur in the immediate postprocedural period. In the PARTNER trial cohort A, 58% of all strokes occurred within the first 48 h and 75% in the first five days.[2] With increasing experience and improved technology, there has been a reduction in the incidence of periprocedural strokes. In addition, the efficacy of embolic protection devices for the prevention of clinically significant strokes during TAVR is currently undergoing clinical testing. Despite initial speculations regarding differences in the stroke risk between BEV and SEV, a recently published large meta-analysis failed to demonstrate any significant difference in the incidence of stroke at 30-day follow-up after BEV and SEV implantation.[25] Similarly, there is no demonstrable difference in stroke risk from different access routes.[25]

Paravalvular aortic regurgitation

Moderate/severe PAR has been shown to be associated with adverse clinical outcomes, including higher mortality on long-term follow-up.[26] Whether the degree of PAR is responsible for an early mortality or is merely a marker for adverse outcomes is not currently clear. Even mild PAR in the PARTNER trial (cohort A) was shown to be associated with increased 1-year to 2-year mortality compared with those with no or trace PAR, underscoring the need for eliminating post-TAVR PAR.[26] Several mechanisms have been implicated in the causation of PAR following TAVR. Prosthesis undersizing is a frequent cause of significant PAR. Second, incorrect positioning of the valve prosthesis (too high or too low) with respect to the annulus can also result in significant PAR, with the failure of the prosthetic skirt to effectively seal the annulus. Third, the aorta-LVOT angle may be important for proper seating of the valve (especially for SEV) within the aortic root, with an increased angle favouring PAR following implantation. In addition, there has been some concern raised about the higher incidence of PAR following SEV implantation compared with BEV implantation, as demonstrated in the CHOICE trial.[19] The treatment of PAR is dependent on the mechanism. Balloon postdilatation and device oversizing might help mitigate the risk of residual AR if the device is underexpanded or undersized. If the device (particularly CoreValve) is implanted too low, snaring may be attempted. Sometimes, a 'valve-in-valve' implantation may be necessary, particularly in cases of high or low implantation of devices. Furthermore, for borderline aortic annulus dimensions, valve sizing may be especially challenging as undersizing may increase the risk of PAR and valve embolisation, whereas oversizing may increase the risk of aortic annular rupture and coronary occlusion. Recently, Binder *et al*[27] have described a strategy to manage these borderline cases by intentionally underexpanding BEVs, thereby minimising the risks of excessive oversizing but maintaining favourable haemodynamics.

Edwards Lifesciences as well as Medtronic are developing new-generation valve systems aimed to improve valve positioning and reduce residual PAR. Edwards SAPIEN III incorporates a distal flex mechanism and fine positioning control for accurate placement and additional cuff to reduce the occurrence of AR. The CoreValve Evolut R has been designed to possess a retrievable/repositionable system to facilitate precise positioning and an extended skirt with modified cell geometry to reduce the risk of PAR. In addition to these new-generation valves, there are several other devices that are undergoing clinical studies. These include Direct Flow Medical Device (Direct Flow Medical, Santa Rosa, California, USA), JenaValve (Jena Valve, Munich, Germany), St Jude's portico valve (St Jude Medical, St Paul, Minnesota, USA) and Symetis Accurate (Symetis SA, Ecublens, Switzerland), which have already received the CE Mark. Repositionability is a common characteristic of most of these new valves that will help increase the implantation quality and reduce the risk of residual PAR. Some of the important characteristics of the second-generation valves are shown in table 2.

Conduction disturbances

New-onset conduction disturbances, particularly new left bundle branch block, occur frequently after TAVR (7%–18% with BEV, 30%–83% with SEV). The need for a new permanent pacemaker implantation following TAVR has been consistently higher after SEV compared with BEV implantation. The greater need for a permanent pacemaker following SEV has been a major challenge for these valves, and efforts are being made to understand and minimise this risk. Initially, a deep valve implantation was believed to be the cause of conduction abnormalities following SEV implantation. However, the rates of pacemaker implantation were significantly higher in the CHOICE trial despite a considerably higher SEV implantation.[19] Although a significantly higher implant depth (~5 mm below the annular plane) was achieved in the CHOICE trial, the investigators also reported a significant degree of oversizing with SEV and the liberal use of the balloon postdilation, which might have contributed to higher conduction abnormalities in the SEV group. The rate of newly implanted permanent pacemakers at 30 days was 17.3% in the BEV group compared with 37.6% in the SEV group.[19]

Vascular complications

With an improvement in experience and reduction in the sheath sizes, the major vascular complications have significantly reduced over the last few years. Importantly, the occurrence of major vascular complications has been shown to be an independent predictor of short-term mortality. Accurate evaluation of the iliofemoral arteries using MDCT or angiography and the use of alternate access other than TF is sometimes necessary to avoid these major complications.[28] In addition, use of fluoroscopically guided access along with angiography from the contralateral side after the haemostasis has been achieved may be very helpful in ensuring that there is no significant vascular damage that needs to be addressed.[28]

COST-EFFECTIVENESS

Evaluating the direct incremental cost-effectiveness of TAVR compared with medical therapy in the PARTNER B trial, TAVR was associated with higher costs during the index hospitalisation, but lower costs during the first year because of fewer repeat hospitalisations.[29] Cumulative costs of TAVR were

Table 1 Incidence of death and stroke at 30 days and 1 year in patients undergoing transcatheter aortic valve replacement across large multicentre registries and randomised controlled trials

Study/N	Period of study	Mean (SD) logistic EuroSCORE	Procedural success (%)	30-day mortality (%)	1-year survival (%)	30-day stroke (%)	1-year stroke (%)
Multicentre registries							
FRANCE 2/3195	1/2010–10/2011	21.9 (14.3)	96.9	9.7	76	3.4	4.1
Canadian/339	1/2005–6/2009	27.7 (16.3)	93.3	10.4	76	2.3	NR
PARTNER-EU/130	4/2007–1/2008	30.0 (13.7)	TF: 96.4 TA: 95.4	TF: 8.2 TA: 18.8	TF: 78.7 TA: 49.3	TF: 3.3 TA: 1.5	TF: 7.0 TA: 10.3
UK-TAVI/ 870	12/2007–12/2009	18.5 (11.7–27.9)*	97.2	7.1	78.6	4.1	NR
Belgian/328	Till 4/2010	28.0 (16.0)	97.0	11.0	CoreValve: 79 Edwards TF: 82 Edwards TA: 63	4.4	NR
FRANCE/244	2/2009–7/2009	26.1 (11.4)	98.4	12.7	NR	3.6	NR
SOURCE/1038	11/2007–1/2009	TF: 25.7 (14.5) TA: 29.1 (16.3)	93.8	8.5	76.1	2.6	4.5
EUROPEAN/646	4/2007–4/2008	23.1 (13.8)	97.2	8.0	NR	1.9	NR
German/697	1/2009–12/2009	20.5 (13.2)	98.4	12.4	NR	2.8	NR
Italian/663	6/2007–12/2009	23.0 (13.7)	98.0	5.4	85.0	1.2	2.5
USA-TVT/7710	11/2011–5/2013	NR	92.0	7.6	NR	2.5	NR
US Extreme Risk Study/489	2/2011–8/2012	22.6 (17.1)	84.6†	8.4	75.7	4.0	7.0
Randomised controlled trials							
PARTNER Cohort A/348	5/2007–8/2009	29.3 (16.5)	NR	3.4	75.8	4.7	6.0
PARTNER Cohort B/179	5/2007–3/2009	26.4 (17.2)	98.8	5.0	69.3	6.7	10.0
US CoreValve High-Risk Study/390	2/2011–9/2012	17.7 (13.1)	98.8	3.3	85.8	4.9	8.8
CHOICE Sapien XT/121	3/2012–12/2013	21.5 (12.9)	95.9†	4.1	NR	5.8	NR
CHOICE CoreValve/120	3/2012–12/2013	22.1 (14.7)	77.5†	5.1	NR	2.6	NR

*Median (Q1–Q3).
†Recorded as device success.
CHOICE, Comparison of Transcatheter Heart Valves in High-Risk Patients with Severe Aortic Stenosis: Medtronic CoreValve vs Edwards SAPIEN XT; FRANCE, French Aortic National CoreValve and Edwards; NR, not reported; PARTNER, Placement of Aortic Transcatheter Valves; PARTNER-EU, Placement of Aortic Transcatheter Valves—European; TA, transapical; TF, transfemoral; UK TAVI, United Kingdom Transcatheter Aortic Valve Implantation; USA TVT, United States of America-Transcatheter Valve Therapy.

significantly higher compared with medical therapy during the first year after the procedure; however, the incremental cost-effectiveness ratio for TAVR per quality-adjusted life year (QALY) gained was located well within the established ranges of willingness-to-pay. Comparing the direct cost-effectiveness of TAVR with SAVR in the PARTNER A trial, similar 1-year costs and QALYs were observed.[30] However, a stratified subanalysis according to access route suggested a considerable difference in

Table 2 Salient characteristics of the new-generation transcatheter aortic valves

Valve	Stent material	Sizes (mm)	Access	Access size (Fr)	Expansion	Repositionable
Edwards SAPIEN 3 (Edwards Lifesciences, California, USA)	Cobalt chromium	20, 23, 26, 29	TF, TA, TAO	14 e sheath	Balloon expandable	No
Edwards CENTERA (Edwards Lifesciences, California, USA)	Nitinol	23, 26	TF	14 e sheath	Self-expandable	Yes
Direct Flow Medical (Direct Flow, Medical, California, USA)	No stent (polyester Fabric cuff)	23, 25, 27, 29	TF, Subclavian	18	Inflation of ring balloons by a polymer	Yes
Heart Leaflet Technologies (Heart Leaflet Technologies, Minnesota, USA)	Nitinol	21, 23	TF	18	Self-expandable	Yes
Innovare (Braile Biomedical, Brazil)	Stainless steel	20, 22, 24, 26, 28	TA	20 (for 20, 22, 24 mm) 22 (for 26, 28 mm)	Balloon-expandable	No
Portico (St. Jude Medical, Minnesota, USA)	Nitinol	23, 25	TF	18	Self-expandable	Yes
JenaValve (JenaValve Technology, Germany)	Nitinol	23, 25, 27	TA	32	Self-expandable	Yes
Sadra Lotus Medical (Boston Scientific, Minnesota, USA)	Nitinol	23, 27	TF	18	Self-expandable	Yes
Symetis Accurate (Symetis, Ecublens, Switzerland)	Nitinol	23, 25, 27	TF, TA	18 (TF) 28 (TA)	Self-expandable	Yes
Engager (Medtronic, Minnesota, USA)	Nitinol	23, 26	TA	28	Self-expandable	Yes
CoreValve Evolut R (Medtronic, Minnesota, USA)	Nitinol	23, 26, 29, 31	TF, TAO, Subclavian	18	Self-expandable	Yes

Fr, French; TAO, transaortic; TA, transapical; TF, transfemoral.

costs during the first year after TAVR when comparing TF and transapical implantation. Transapical TAVR led to higher costs and less quality-adjusted life expectancy compared with SAVR. However, TF TAVR appeared to be attractive from an economical point of view with reduced costs for 1 year after TAVR and higher health-adjusted life expectancy compared with transapical TAVR and SAVR.

FUTURE IMPLICATIONS

Over the last decade, TAVR has emerged as one of the most important innovations in the field of interventional cardiology, with a huge potential to help millions of patients in a safe, minimally invasive manner. Since the inception of TAVR, the interventional cardiology community has been faced with the task of perfecting the skillset and cultivating the infrastructure required to perform this complex procedure in a safe and effective manner. Perhaps, a bigger challenge now is the 'rational dispersion' of this transformative technology into widespread clinical practice, maintaining the excellent results that have been seen in rigorously conducted RCT settings. The upcoming years are going to witness a growth in the choices available to perform TAVR along with the use of TAVR in intermediate and possibly low-risk patients. Repositionability, lower profile, small access and reduction of PAR are going to be the major areas of focus for the newer-generation devices. In addition, one could expect an extension of application of TAVR to bicuspid valves, degenerated bioprosthetic valves and selected patients with pure severe aortic regurgitation. Furthermore, the impact of CAD on outcomes following TAVR remains understudied and needs to be rigorously evaluated in future studies. As the technology continues to mature and our experience continues to evolve, one could expect considerable improvements in patient outcomes in the years to come.

CONCLUSIONS

TAVR is truly a transformative innovation that has provided an effective alternative for the treatment of patients with severe AS who were previously considered inoperable or high risk for SAVR. Although there have been demonstrated benefits in terms of improved survival and quality of life, a significant proportion of patients die of non-cardiovascular causes within a short timespan after the procedure, underscoring the importance of optimal patient selection. With a rapid growth in the TAVR technology, the upcoming years are bound to witness a substantial increase in the choice of valves, smaller access sites and greater use of adjunctive imaging to facilitate safe and effective performance of the procedure across the world.

Acknowledgements We are thankful to Ms Kathryn Brock for editorial assistance on this manuscript.

Contributors All authors meet the criteria for authorship based on their contribution to the manuscript.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Leon MB, Smith CR, Mack M, *et al*. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
2 Smith CR, Leon MB, Mack MJ, *et al*. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–98.
3 Adams DH, Popma JJ, Reardon MJ, *et al*. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790–8.
4 Nashef SA, Roques F, Michel P, *et al*. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16:9–13.
5 O'Brien SM, Shahian DM, Filardo G, *et al*. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2—isolated valve surgery. *Ann Thorac Surg* 2009;88(1 Suppl):S23–42.
6 Goel SS, Ige M, Tuzcu EM, *et al*. Severe aortic stenosis and coronary artery disease—implications for management in the transcatheter aortic valve replacement era: a comprehensive review. *J Am Coll Cardiol* 2013;62:1–10.
7 Yousef A, Simard T, Pourdjabbar A, *et al*. Performance of transcatheter aortic valve implantation in patients with bicuspid aortic valve: systematic review. *Int J Cardiol* 2014;176:562–4.
8 Seiffert M, Bader R, Kappert U, *et al*. Initial German experience with transapical implantation of a second-generation transcatheter heart valve for the treatment of aortic regurgitation. *JACC Cardiovasc Interv* 2014;7:1168–74.
9 Dvir D, Webb JG, Bleiziffer S, *et al*. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA* 2014;312:162–70.
10 Carabello BA. Low-gradient, low-ejection fraction aortic stenosis: what we know and what we do not know. *JACC Cardiovasc Interv* 2012;5:560–2.
11 Gotzmann M, Lindstaedt M, Bojara W, *et al*. Clinical outcome of transcatheter aortic valve implantation in patients with low-flow, low gradient aortic stenosis. *Catheter Cardiovasc Interv* 2012;79:693–701.
12 O'Sullivan CJ, Stortecky S, Heg D, *et al*. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. *Eur Heart J* 2013;34:3437–50.
13 Arnold SV, Reynolds MR, Lei Y, *et al*. Predictors of poor outcomes after transcatheter aortic valve replacement: results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. *Circulation* 2014;129:2682–90.
14 Arnold SV, Spertus JA, Lei Y, *et al*. How to define a poor outcome after transcatheter aortic valve replacement: conceptual framework and empirical observations from the placement of aortic transcatheter valve (PARTNER) trial. *Circ Cardiovasc Qual Outcomes* 2013;6:591–7.
15 Lindman BR, Alexander KP, O'Gara PT, *et al*. Futility, benefit, and transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2014;7:707–16.
16 Stortecky S, Schoenenberger AW, Moser A, *et al*. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2012;5:489–96.
17 Kapadia SR, Svensson LG, Roselli E, *et al*. Single center TAVR experience with a focus on the prevention and management of catastrophic complications. *Catheter Cardiovasc Interv* 2014;84:834–42.
18 Motloch LJ, Rottlaender D, Reda S, *et al*. Local versus general anesthesia for transfemoral aortic valve implantation. *Clin Res Cardiol* 2012;101:45–53.
19 Abdel-Wahab M, Mehilli J, Frerker C, *et al*. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. *JAMA* 2014;311:1503–14.
20 Sherif MA, Abdel-Wahab M, Stocker B, *et al*. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. *J Am Coll Cardiol* 2010;56:1623–9.
21 Wong DT, Bertaso AG, Liew GY, *et al*. Relationship of aortic annular eccentricity and paravalvular regurgitation post transcatheter aortic valve implantation with CoreValve. *J Invasive Cardiol* 2013;25:190–5.
22 Tuzcu EM, Kapadia SR. Selection of valves for TAVR: is the CHOICE clear? *JAMA* 2014;311:1500–02.
23 Mohr FW, Holzhey D, Mollmann H, *et al*. The German Aortic Valve Registry: 1-year results from 13 680 patients with aortic valve diseasedagger. *Eur J Cardiothorac Surg* 2014;46:808–16.
24 Agarwal S, Tuzcu EM, Stewart W, *et al*. Comparison of multicenter registries and randomized control trials for transcatheter aortic valve replacement (TAVR). *Indian Heart J* 2013;65:400–11.
25 Athappan G, Gajulapalli RD, Sengodan P, *et al*. Influence of TAVR strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. *J Am Coll Cardiol* 2014;63:2101–10.
26 Kodali SK, Williams MR, Smith CR, *et al*. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2012;366:1686–95.
27 Binder RK, Webb JG, Willson AB, *et al*. The impact of integration of a multidetector computed tomography annulus area sizing algorithm on outcomes of transcatheter aortic valve replacement: a prospective, multicenter, controlled trial. *J Am Coll Cardiol* 2013;62:431–8.
28 Krishnaswamy A, Parashar A, Agarwal S, *et al*. Predicting vascular complications during transfemoral transcatheter aortic valve replacement using computed tomography: a novel area-based index. *Catheter Cardiovasc Interv* 2014;84:844–51.
29 Reynolds MR, Magnuson EA, Wang K, *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;125:1102–9.
30 Reynolds MR, Magnuson EA, Lei Y, *et al*. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (Cohort A). *J Am Coll Cardiol* 2012;60:2683–92.

Heart

Transcatheter aortic valve replacement: current perspectives and future implications

Shikhar Agarwal, E Murat Tuzcu, Amar Krishnaswamy, Paul Schoenhagen, William J Stewart, Lars G Svensson and Samir R Kapadia

Heart published online November 19, 2014