

Transcatheter Aortic Valve Implantation

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1. Introduction

Calcific aortic stenosis (AS) is the most common form of degenerative heart valve disease in developed countries. AS predominantly affects the elderly with a prevalence of 4% in people over the age of 80 years. With increasing longevity and an ageing population the absolute number of people afflicted with AS is set to rise. The clinical course of the disease is insidious at first (Ross & Braunwald, 1968), but is followed by rapid progression once symptoms of congestive cardiac failure, angina and syncope develop (Cheitlin *et al.*, 1979; Otto *et al.*, 1989; Davies *et al.*, 1991; Peter *et al.*, 1993). If left untreated mortality exceeds 50% at two years (Kelly *et al.*, 1988; Turina *et al.*, 1987) and AS is, therefore, set to become a major public health problem in the ensuing decades.

Aortic valve replacement (AVR) has been the gold standard intervention for AS for more than 40 years (Charlson *et al.*, 2006) and over 60,000 procedures are performed annually in the European Union. However, one third of patients are denied access to surgery, often due to their advanced age (Lung *et al.*, 2003, 2005). Percutaneous balloon valvuloplasty was heralded initially as a promising breakthrough for high-risk symptomatic patients with AS (Cribier *et al.*, 1986). However, long-term follow-up has yielded unacceptable rates of restenosis and poor event-free survival (Otto *et al.*, 1994; Lieberman *et al.*, 1995). Balloon valvuloplasty is now recommended only as a bridge to emergency AVR or in the palliation of symptoms in the frailest of patients (Ussia *et al.*, 2010; Zahn *et al.*, 2011).

Transcatheter aortic valve implantation (TAVI) has recently emerged as an effective therapeutic alternative to conventional AVR for high-risk AS patients. TAVI was developed initially in porcine models (Anderson *et al.*, 1992), but it took a decade for this technology to be translated to humans (Cribier *et al.*, 2002). Initially, an antegrade transseptal approach was used, but this has now been superseded by transapical (Ye *et al.*, 2006; Webb *et al.*, 2007) and retrograde percutaneous techniques (transarterial or transaxillary) (Webb *et al.*, 2006). The range of different approaches has increased the feasibility of TAVI in patients with relative contraindications, such as extensive peripheral vascular disease, porcelain aorta and thoracic radiotherapy. TAVI is also less invasive than open AVR and permits replacement of the native diseased valve in the beating heart without the need for sternotomy and cardiopulmonary bypass. Consequently, TAVI may be less influenced by a patient's comorbidities and may facilitate faster recovery.

A multidisciplinary team consisting of interventional cardiologists, cardiothoracic surgeons, cardiac anaesthetists and imaging specialists is best suited to make decisions between open

AVR, TAVI and medical management. This ensures apt patient selection and prompt delivery of care. There has been a rapid expansion in the number of studies investigating TAVI in the last five years and these have demonstrated promising results in terms of feasibility, safety and efficacy. Doubts remain, however, about the long-term durability of TAVI implants and their disposition to valvular dysfunction and about the need for reoperation. This chapter discusses the selection of patients for TAVI, techniques of implantation, clinical and patient-reported outcomes and future directions of research and development.

2. Patient selection

Clinical decision-making in patients with AS is complex and from the outset requires a patient-centered approach and the involvement of a multidisciplinary team. Open AVR is associated with excellent clinical and functional outcomes in large modern series (Brown *et al.*, 2009; Malaisrie *et al.*, 2010) and, at present, is the gold standard intervention for patients with severe, symptomatic AS (Bonow *et al.*, 2006). However, patient selection is controversial. Central to the controversy is a belief that elderly patients, especially those with major comorbidities or with complications of AS (e.g. left ventricular dysfunction) present too great an operative risk or lack sufficient life expectancy to justify surgical AVR (Asimakopoulos *et al.*, 1997; Connolly *et al.*, 2000; Elayda *et al.*, 1993; Monin *et al.*, 2003). AVR is highly invasive and requires sternotomy, cardiopulmonary bypass, hypothermic cardioplegic arrest and cardiotomy. These factors expose patients to certain deleterious effects on end-organs, including ischemia, reperfusion injury, systematic inflammatory response, surgical trauma and oxidative stress (Anselmi *et al.*, 2004). In 2003, the Euro Heart Survey on Valvular Heart Disease reported that approximately one third of patients with severe, symptomatic AS are denied potentially life-saving surgery because of concerns over age, comorbidities and likely longevity (Iung *et al.*, 2003, 2005). This is in spite of some recent series demonstrating promising safe and efficacious outcomes for AVR in octogenarians (Melby *et al.*, 2007; Florath *et al.*, 2010; Leontyev *et al.*, 2009).

TAVI is a novel approach to AS in high-risk patients and provides an alternative management option that negates invasive surgery. TAVI is still in its infancy in terms of the operator learning curve, the level of technological development of the implants and the evidence base required to determine which patients are most likely to benefit. At present, TAVI is recommended only for patients not considered suitable for open AVR and who have a life expectancy of greater than one year (Vahanian *et al.*, 2008). This section will describe some of the available patient risk stratification tools used for clinical decision-making in AS, the current indications and contraindications to TAVI, and possible diversification in the use of minimally invasive aortic valve interventions.

2.1 Risk stratification tools

The choice between treatment options in AS should ideally be based upon a shared decision between the fully informed patient and a multidisciplinary team who guide the patient to the required information. Part of this process includes an assessment by physicians of the likely risk of mortality and serious morbidity of undergoing open AVR. A range of scoring systems have been developed that are designed to assist surgeons in such risk stratification (Ambler *et al.*, 2005; Edwards *et al.*, 2001; Florath *et al.*, 2003; Hattler *et al.*, 1994; Higgins *et al.*,

1992; Nashef *et al.*, 1999; Nowicki *et al.*, 2004; O'Brien *et al.*, 2009; Parsonnet *et al.*, 1989; Pons *et al.*, 1997; Roques *et al.*, 1995; Roques *et al.*, 1999; Tremblay *et al.*, 1993; Tu *et al.*, 1995). These systems are usually derived from multivariate analyses of preoperative and operative variables believed to influence outcomes in large cohorts of cardiothoracic patients. Risk stratification tools may be either generic for all open cardiothoracic procedures or specific to heart-valve interventions. The focus of this subsection is to discuss some of the widely used risk stratification tools.

The Parsonnet score was one of the first mortality indicators developed to calculate average risk estimates of death in adult cardiothoracic patients (Parsonnet *et al.*, 1989). The model allocates "additive" points for 14 risk factors associated with perioperative mortality, which are subsequently used to assign a percentage probability of death. The factors include female gender, obesity, diabetes, hypertension, low ejection fraction, increased age, first or second reoperation, preoperative intra-aortic balloon pump, emergency presentation from the cardiac catheter laboratory, dialysis dependency, catastrophic clinical state, valve surgery and combined valve surgery and coronary artery bypass grafts (CABG). In addition to overestimating mortality in high-risk cases, the Parsonnet score has been criticized for being subjective and including some factors that are now known not to be linked to early postoperative death (Gabrielle *et al.*, 1997). The Parsonnet score also omits other potentially important factors, such as the urgency of surgery, which is widely considered to be strongly associated with perioperative outcome (Wynne-Jones *et al.*, 2000).

The Parsonnet score has been superseded by the European System for Cardiac Operative Risk Evaluation (EuroSCORE). The EuroSCORE was developed by analyzing survival outcomes for 19,030 cardiac surgical patients in eight European countries (Roques *et al.*, 1999). Logistic regression was used to reduce a list of 97 potential postoperative mortality risk factors to 18 independent variables with odds ratios of >1 predictive of death. It bears many similarities to the Parsonnet system and involves calculation of percentage predicted mortality by addition of points ascribed to various risk factors to produce an "additive" mortality score (Table 1). For AVR, the EuroSCORE study reported an overall procedural mortality of 6% and mortality in the absence of risk factors of 1.1%. The precision and accuracy of the EuroSCORE has been demonstrated in numerous studies (Kobayashi *et al.*, 2009; Wendt *et al.*, 2010), but it has several limitations that compromise its validity in sufferers of severe, symptomatic AS. First, the data is derived from patients undergoing cardiac surgery for heterogeneous indications, including a high percentage of cases of isolated coronary artery bypass grafts (63.9%). Risk factors are, therefore, not specific to AVR. Secondly, there is evidence that the EuroSCORE overestimates mortality in high-risk patients or is inaccurate in those with unusual combinations of risk factors (Brown *et al.*, 2008; Dewey *et al.*, 2008). This can exaggerate mortality estimates and may mean that patients are not offered AVR, even if they are potential surgical candidates. The "logistic" EuroSCORE has since been introduced for use in high-risk individuals because of its greater accuracy (Roques *et al.*, 2003). Nonetheless, it still suffers from problems with clinical relevance. Consequently, the "additive" and "logistic" algorithms have been combined to form the "modified" EuroSCORE (Nissinen *et al.*, 2009). Further problems with the EuroSCORE relate to the fact that it does not take into account local institutional outcomes (Vahanian *et al.*, 2008) or characteristics unique to certain AS patients (e.g. previous CABG with patent grafts, porcelain aorta or thoracic radiotherapy). These factors may confer additional risks that can alter the choice of intervention at the institutional level (Robes-Cabau *et al.*, 2010).

Variable	Odds ratio \pm Standard error	P-value	Additional % mortality
Age per 5 years after 60 years	1.1 \pm 0.007	0.001	1
Female gender	1.4 \pm 0.128	0.001	1
Preoperative creatinine > 200 μ mol/L	1.9 \pm 0.256	0.001	2
Extracardiac arteriopathy	1.9 \pm 0.376	0.001	2
Pulmonary disease	1.6 \pm 0.284	0.006	1
Neurological dysfunction	2.3 \pm 0.584	0.001	2
Previous cardiac surgery	2.6 \pm 0.324	0.001	3
Recent myocardial infarction	1.6 \pm 0.208	0.001	2
LVEF 30-50%	1.5 \pm 0.138	0.001	1
LVEF < 30%	2.5 \pm 0.340	0.001	3
Pulmonary hypertension (> 60 mmHg)	2.0 \pm 0.423	0.001	2
Active endocarditis	2.5 \pm 0.678	0.001	3
Unstable angina	1.5 \pm 0.202	0.001	2
Emergency operation	2.8 \pm 0.440	0.001	2
Critical perioperative condition	2.2 \pm 0.319	0.001	3
Ventricular septal rupture	3.8 \pm 1.735	0.002	4
Noncoronary surgery	1.6 \pm 0.170	0.001	2
Thoracic aortic surgery	3.2 \pm 0.650	0.001	3

Table 1. Risk factors for mortality in patients undergoing cardiac surgery based on the EuroSCORE dataset (reproduced from Roques *et al.*, 1999; LVEF = left ventricular ejection fraction)

Recently, emphasis has been placed on developing risk stratification tools with greater reliability and validity in patients with valvular heart disease. The Ambler score was published in 2005 after it had been field-tested in 32,839 consecutive patients undergoing heart valve surgery in the UK (Ambler *et al.*, 2005). It identified 14 risk factors associated with in-hospital mortality (operative priority, age, renal failure, operation sequence, ejection fraction, concomitant tricuspid valve surgery, type of valve surgery, concomitant CABG, body mass index, preoperative arrhythmia, diabetes, gender, and hypertension). Its development involved robust methodology in a large cohort of patients, but it has not been widely adopted, perhaps because of concerns over external validity in non-UK populations. The Society of Thoracic Surgeons has since built on the advantages of the Ambler score by producing a tool that assists in predicting nine different postoperative variables (STS-PROM; O'Brien *et al.*, 2009). These are mortality, permanent stroke, renal failure, prolonged ventilation, deep sternal wound infection, reoperation, a composite endpoint of mortality and major morbidity, and short and prolonged postoperative stay. In addition to extending predictive models to several causes of major morbidity, the STS-PROM has been shown to be more reliable than the EuroSCORE in estimating mortality in high-risk patients (Dewey *et al.*, 2008). At present, most major studies involving the selection of patients for TAVI use the EuroSCORE and STS-PROM.

2.2 Indications and assessment of suitability for TAVI

TAVI is recommended for use only in patients with calcified pure or predominant AS, and not in cases where aortic regurgitation is the primary pathology. In 2008, the European

Association of Cardiothoracic Surgery (EACTS), the European Society of Cardiology (ECS), and the European Association of Percutaneous Cardiovascular Intervention (EAPCI) issued a joint statement describing a four-stage assessment procedure to be undertaken to differentiate between treatment options in AS and to confirm suitability for TAVI (Vahanian *et al.*, 2008). The first stage involves echocardiography to confirm the diagnosis and severity of AS, and to exclude significant aortic regurgitation. TAVI is presently restricted to cases of severe AS because of the proven effectiveness of AVR. The inclusion criteria of well-designed trials offer some insight into the definition of the severity of AS at echocardiography. In THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial, patients were randomized to interventions (AVR, TAVI, or medical management) only if proved to have an aortic valve area (AVA) of $< 0.8 \text{ cm}^2$ (or an indexed AVA of $< 0.6 \text{ cm}^2$) or a peak aortic valve gradient of $> 40 \text{ mmHg}$ (or a peak velocity of $> 4.0 \text{ m/s}$) (Leon *et al.*, 2010). Analogous values should be used when deciding whether TAVI is appropriate for particular individuals, and many studies have used similar cut-offs to assign patients to treatment with TAVI (Clavel *et al.*, 2010; Malaisrie *et al.*, 2011; Zahn *et al.*, 2011). In certain circumstances, low-dose dobutamine echocardiography may also be of value to distinguish between severe AS and the rare “pseudo-severe” AS, especially in patients with a low left ventricular (LV) ejection fraction and a low aortic transvalvular gradient (Bonow *et al.*, 2006; Vahanian *et al.*, 2007).

The second stage in TAVI assessment involves an accurate evaluation of the presenting symptoms and clinical findings. Current guidelines recommend that TAVI should be undertaken only when symptoms are directly attributable to AS (Vahanian *et al.*, 2008). Several concurrent diseases may mimic the symptom profile of AS, such as chronic obstructive pulmonary disease or pulmonary hypertension. A clear history and chronology of the symptoms of dyspnea, chest pain, and syncope are, therefore, required, and when the diagnosis is uncertain, biomarkers of increased myocardial mechanical load, such as beta-type natriuretic peptide (BNP), may be of value (Vahanian *et al.*, 2010). Clinical confirmation of the diagnosis is necessary because of concerns over the long-term durability of TAVI devices.

Arguably, the most complex stage when assessing patients with AS is deciding between AVR, TAVI, and conservative management. This requires multidisciplinary team evaluation of the possible risks of open AVR and TAVI, predicted life expectancy, and quality of life. To evaluate the risk of operative mortality and serious morbidity, it is recommended that clinical judgment be combined with the scores from two risk stratification tools (Vahanian *et al.*, 2008). This combination allows for an objective risk assessment, while ensuring that additional factors not included in risk stratification tools (e.g. porcelain aorta, previous CABG with patent grafts, previous thoracic radiotherapy, or liver cirrhosis) are taken into account. Typically, mortality $> 20\%$ calculated using the logistic EuroSCORE or $> 10\%$ using the STS-PROM are seen as high-risk indicators that would preclude open AVR in most cases (Leon *et al.*, 2010; Vahanian *et al.*, 2008; Vahanian *et al.*, 2010). However, scoring systems should not necessarily be viewed as a substitute for experienced clinical judgment or informed patient choice. As part of the multidisciplinary approach, it is recommended that patient-reported outcomes, such as health-related quality of life (HRQL), be considered. The use of validated HRQL tools should be combined with clinical parameters to assist in the shared decision-making process (Lee *et al.*, 2006; Vahanian *et al.*, 2008).

The final stage before TAVI insertion in high-risk patients with severe, symptomatic AS includes an assessment of the feasibility and contraindications to TAVI. The first-line

investigation is coronary angiography to identify occlusive lesions in need of revascularization. Lesions amenable to percutaneous angioplasty and stenting can be treated either before, during, or after TAVI. The decision on the timing of revascularization is complex and should be tailored to individual cases. Patients with proximal coronary stenoses may not be appropriate candidates for TAVI (Vahanian *et al.*, 2008) because of concerns over occlusion of the coronary ostia by the device (Gogas *et al.*, 2011; Gurvitch *et al.*, 2011). If coronary stenoses can be managed only surgically, then a choice must be made between high-risk AVR and the poor outcomes associated with medical management and balloon valvuloplasty.

Determining the diameter of the aortic annulus is a prerequisite to TAVI operational planning and ensures that an appropriately sized implant is deployed. This can be accomplished using either invasive techniques (e.g. aortography as part of balloon valvuloplasty) or noninvasive imaging modalities (e.g. echocardiography, multislice high resolution computed tomography, or magnetic resonance imaging) (Tops *et al.*, 2008; Vahanian *et al.*, 2008). Transthoracic echocardiography has been shown to underestimate the size of the aortic annulus, and should be supplemented with transesophageal echocardiography when borderline sizes result in doubt over the feasibility of the procedure (Moss *et al.*, 2008). Accurate sizing prior to TAVI is necessary to prevent paravalvular leak and rupture of the aortic annulus. The peripheral vasculature must also be imaged, in particular the aortic arch, descending aorta, and iliac vessels. This can be achieved with either formal or computed tomography angiography. Gadolinium magnetic resonance angiography is an alternative in patients with impaired renal function. Both the size and tortuosity of the vessels are important because they affect access and help to decide between the transarterial and transapical approaches.

2.3 Contraindications to TAVI

For technical reasons, TAVI is not possible in all high-risk patients with AS, but using different access ports has increased the number of patients who can be successfully treated. General contraindications to TAVI include:

- Aortic annulus diameter < 18 mm or > 25 mm for balloon expandable implants, and < 20 mm or > 27 mm for self-expandable devices.
- Bicuspid aortic valves that may lead to incomplete deployment of the device and paravalvular leak (Zegdi *et al.*, 2008).
- Heavy asymmetrical aortic valve calcification because of concerns over occlusion of the coronary ostia (Webb *et al.*, 2006).
- Low position of the coronary ostia (< 8 mm from the aortic annulus).
- Aortic root diameter of > 45 mm at the aorto-tubular junction for self-expandable devices.
- Severe organic mitral regurgitation.
- LV thrombus.

There are a number of contraindications specific to the type of approach. For the transfemoral approach, these are:

- Severely calcified or tortuous iliac arteries.
- Iliac artery diameter of < 6 mm to < 9 mm, depending on the type of device used.
- Previous aorto-femoral bypass grafts.
- Severely angulated aorta or atherosclerotic aortic arch.

- Transverse ascending arch (for balloon expandable devices).
- Aortic aneurysm with extensive mural thrombus.
- Coarctation of the aorta.

For the transapical approach, contraindications are:

- Previous surgical patch of the left ventricle (e.g. Dor procedure).
- Calcified pericardium.
- Severely impaired respiratory function.
- Inability to access the apex of the left ventricle due to anatomical constraints (e.g. chest deformity).

2.4 Expanding the role of TAVI

Implants used in open AVR are either mechanical or bioprosthetic. Mechanical valves have the advantage of long-term durability, but require life-long anticoagulation with the associated risk of major hemorrhage. Patients fitted with bioprosthetic valves do not need to take anticoagulants, but the chance of valvular degeneration increases with time. Mechanical valves are, therefore, usually restricted to younger patients, while bioprosthetic implants are used more frequently in the elderly population, in which the chance of surviving to revision surgery is low. Nonetheless, valvular degeneration occurs in a proportion of patients, and treatment typically necessitates revision AVR, which is inherently high-risk.

In 2008 the first case of valve-in-valve (VIV) TAVI was reported in an 82-year-old patient with valvular degeneration of a Carpentier-Edwards Perimount aortic valve (Walther *et al.*, 2008a). This pioneering procedure was performed off-pump using a transapical approach. VIV is an attractive technique that involves placing the implant within the previous prosthetic valve, abutting the degenerated valve leaflets up against the aortic annulus. Typically, transapical access is preferred for VIV procedures, although reports have recently emerged describing the transaxillary (Sharp *et al.*, 2010) and trans-subclavian approaches (Olsen *et al.*, 2010). The Edwards SAPIEN valve may be better suited to VIV implantation (Kempfert *et al.*, 2010), although the Medtronic CoreValve system has been successfully used (Khawaja *et al.*, 2010).

There are promising early results for VIV, although reports tend to be anecdotal or restricted to small case series, and no large comparative studies are currently available (Ferrari *et al.*, 2010; Kempfert *et al.*, 2010; Khawaja *et al.*, 2010; Olsen *et al.*, 2010; Sharp *et al.*, 2010). Transvalvular gradients post-procedure are usually satisfactory (Ferrari *et al.*, 2010; Kempfert *et al.*, 2010; Walther *et al.*, 2008a), while residual aortic regurgitation tends to be minimal (Kempfert *et al.*, 2010). Severe paravalvular leak is a feared complication of TAVI, but several authors have described its successful treatment with rescue VIV (Rodes-Cabau *et al.*, 2009; Taramasso *et al.*, 2010). Concerns exist over excessive transvalvular gradients of VIV implants in patients fitted previously with small-diameter prostheses (e.g. < 23 mm in diameter) (Ferrari *et al.*, 2010). For TAVI, the diameter of the device is typically oversized by 10-20% in relation to the aortic annulus, but for VIV undersizing is preferred, which is currently not feasible in some patients with small annuli because of the size of available implants. At present, VIV is off-label in many countries, including the United States.

TAVI is minimally invasive and has consistently demonstrated promising outcomes in high-risk patients (see Section 4). In the future, it is likely that the indications for TAVI will be expanded to include younger patients at low operative risk. However, caution is advised for

several reasons. Despite the lack of randomized clinical trial (RCT) data to support the use of open surgery, AVR has shown excellent long-term clinical, hemodynamic and functional outcomes in low-risk AS patients (Hammermeister *et al.*, 1993; Myken *et al.*, 1995; Peterseim *et al.*, 1999). Modern RCTs comparing AVR to medical management would be unethical because of a lack of clinical equipoise, leading to appropriate patients being denied access to a treatment with proven long-term effectiveness. The durability of TAVI implants is still a concern due to the technique's relative age. More work to characterize the long-term outcomes of TAVI is necessary before it is offered routinely to low-risk patients.

3. Devices and techniques

The technology that underpins TAVI has evolved dramatically in the last two decades since its inception in animal models (Anderson *et al.*, 1992) and later realization in humans (Cribier *et al.*, 2002). At present, there are two major producers of TAVI devices that are used routinely in clinical practice (Edwards Lifesciences, Irvine, CA, USA & Medtronic Inc., Minneapolis, MN, USA). Technological development of both implants is on-going, and each has its advantages and disadvantages in different clinical situations. There are a variety of access sites through which TAVI can be performed, including directly through the left ventricular apex as well as the femoral, axillary and subclavian arteries. This section will describe the features of current and future implants and the techniques required for their implantation.

3.1 TAVI devices

The prototypic Cribier-Edwards TAVI device was one of the earliest deployed in humans. It has now been replaced by newer Edwards Lifesciences designs, including the SAPIEN transcatheter heart valve (THV) (Figure 1) and, more recently, by the SAPIEN XT. The SAPIEN devices are constructed from bovine pericardial leaflets mounted on a cobalt-chromium frame. The device is balloon expandable and manufactured in 23-mm and 26-mm sizes, which allows it to be used in patients with aortic annulus diameters of between 18 mm and 25 mm. As the implant is deployed (Figure 2), it fixes within the aortic annulus without the need for stabilization in the ascending aorta (Webb and Cribier, 2010). Early devices required large-caliber delivery systems; however, the latest versions can be deployed through vessels with a minimum diameter of 6 mm. Transapical and percutaneous approaches can both be used with the SAPIEN system.

The Medtronic CoreValve consists of a porcine pericardial valve mounted on a nitinol self-expandable metal frame. It is considerably longer than SAPIEN devices (53-55 mm versus 15-17 mm) and anchors distally in both the ascending aorta and supracoronary region. The CoreValve can be deployed through an access channel with a minimum diameter of 6 mm and can be used in patients with an aortic annulus diameter of between 20 mm and 27 mm. The device is not licensed for transapical use, but when used via a peripheral access vessel, it is associated with greater hemodynamic stability during deployment, more forgiving positioning and can be retrieved if sited incorrectly (Webb and Cribier, 2010). Despite this, the CoreValve suffers from a high incidence of post-procedural heart block, which requires prolonged cardiac monitoring, and pacemaker insertion is necessary in up to 40% of cases. A number of next generation TAVI devices are currently undergoing clinical testing (Falk *et al.*, 2009; Low *et al.*, 2008; Schofer *et al.*, 2008; Treede *et al.*, 2010). These are based generally on the self-expandable CoreValve system and allow for smaller caliber delivery systems,

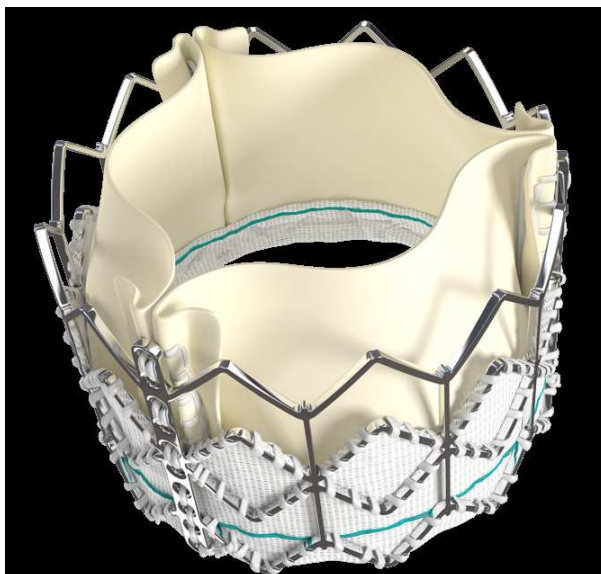


Fig. 1. The Edwards SAPIEN Transcatheter aortic valve (Photo courtesy of Edwards Lifesciences)



Fig. 2. Transcatheter aortic valve crimped onto the introducing catheter (Photo courtesy of Edwards Lifesciences)

retrieval and greater accuracy when deployed. Examples include the DirectFlow (Direct Medical Flow Inc., Santa Rosa, CA, USA), Lotus (Boston Scientific Inc., Natick, MA, USA) and HLT (Heart Leaflet Technologies Inc., Maple Grove, MN, USA). Other systems incorporate features that allow fixation in the supracoarony aorta (Accurate, Symentis Inc., Lausanne, Switzerland; St Jude, St Jude Medical Inc., St. Paul, MN, USA) and anatomical guides to demonstrate the position of the native valve and coronary arteries, thus facilitating deployment (Engager, Medtronic Inc., USA; JenaClip, JenaValve Inc., Munich, Germany). At present, little is known about these novel valves in terms of their efficacy, safety, feasibility, and long-term durability. Further work is required to characterize their outcomes before they can be recommended for use in routine clinical practice.

3.2 Percutaneous access

Initial reports of TAVI used a transeptal approach with access via the venous system (Cribier *et al.*, 2002). This route was technically challenging and not reproducible. Retrograde arterial approaches are now much more widely used. Access is gained typically through the femoral

artery (Webb *et al.*, 2006). The axillary, subclavian, and retroperitoneal iliac arteries, as well as the ascending aorta, have also been successfully used (Webb and Cribier, 2010). Cut-down to expose the arteries is sometimes done: this improves the ease of cannulation of the vessels and ensures safe closure. In such cases, the patient is usually anesthetized, which confers additional risks in this frail population. Percutaneous arterial puncture and suture closure is now the standard of care and can be completed safely under sedation (De Jaegere *et al.*, 2007; Vavuranakis *et al.*, 2010). After arterial puncture, aortography is done to characterize the coronary vessels, diseased valve, and aorta. Balloon valvuloplasty is then used to dilate the native valve under rapid ventricular pacing, which decreases cardiac output while the balloon is inflated. Between periods of rapid pacing, the blood pressure must be allowed to normalize. Intraoperative imaging, including aortography, transesophageal echocardiography, and fluoroscopy, is used to identify the optimal position for the new valve. Once this has been determined, the valve is deployed. Rapid ventricular pacing is required for balloon expandable devices (Figure 3), but not for self-expandable systems. Post-procedural echocardiography and aortography are done to check the position and function of the implant, the patency of the coronary vessels, and the presence of early complications (e.g. aortic regurgitation, paravalvular leak, aortic dissection, hemopericardium). It is recommended that patients are nursed postoperatively in the cardiac intensive care unit with invasive monitoring.

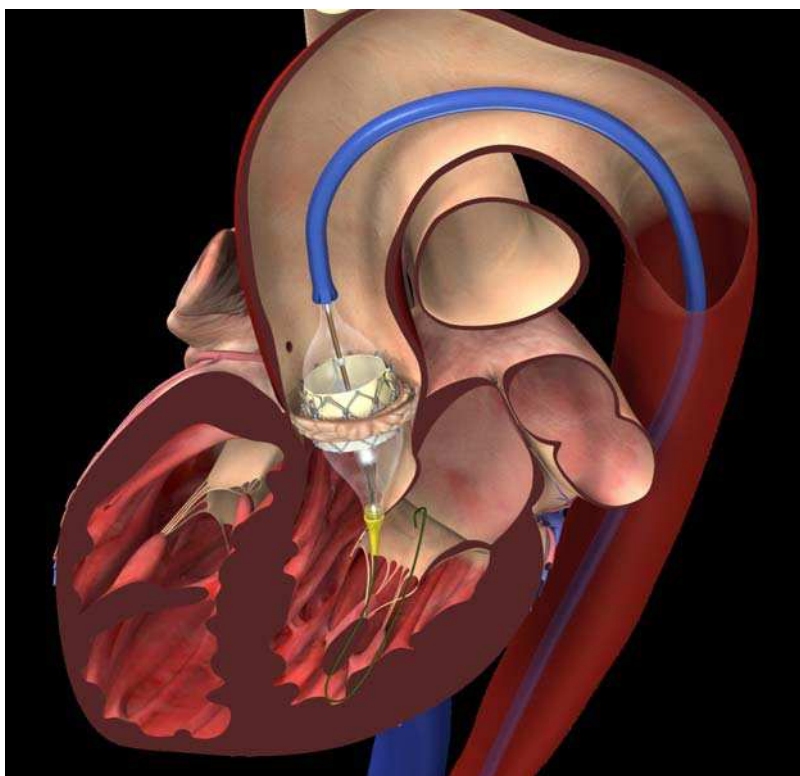


Fig. 3. Showing the retrograde approach and balloon inflation (black arrow) of the transcatheter aortic valve (white arrow) (Photo courtesy of Edwards Lifesciences)

3.3 Transapical approach

Transapical TAVI involves inserting the valve device in an antegrade fashion through the anterolateral chest wall and apex of the left ventricle (Figure 4). This is done under general anesthesia with cardiopulmonary bypass (CPB) on standby. CPB is usually established through the femoral vessels if required. The site of the incision is determined by transthoracic echocardiography. After the chest cavity has been entered, the pericardium is opened and secured to the thoracic wall. Pacing wires are then attached to the myocardium to facilitate rapid ventricular pacing. Two purse-string sutures are inserted into the apex, and an introducer sheath is passed between them into the left ventricle. Guided by imaging, the implant is positioned across the native valve and then deployed using balloon inflation and rapid ventricular pacing. Postoperatively, the patient should be nursed in an intensive care unit for at least 24 hours. Transapical TAVI involves a thoracotomy, and for this reason is not recommended for patients with severe respiratory disease that precludes one-lung ventilation. In rare instances, a mini-sternotomy has been combined with retrograde transaortic TAVI, where the device is inserted via the ascending aorta (Latsios *et al.*, 2010). This technique is reserved for patients with no other access sites.

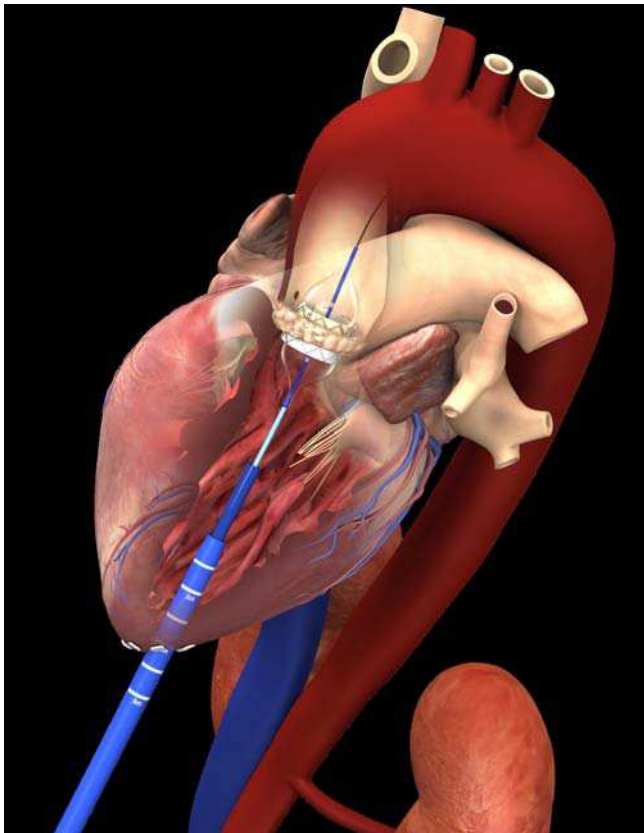


Fig. 4. Trocar being antegradely introduced through the apex of the left ventricle (Photo courtesy of Edwards Lifesciences)

3.4 Service structure

The performance of TAVI should be restricted to a small number of high-volume centers with readily available input from specialist cardiothoracic surgeons, interventional cardiologists, cardiac anesthetists, intensivists and perfusionists. The center must be proficient in dealing with both open and percutaneous valvular interventions in high-risk populations. Familiarity with the procedure and multidisciplinary management are likely to improve the rate of successful implantation and limit the number of complications. Furthermore, if complications do occur, they can be managed without the delay associated with transferring patients to another institution. Interventional cardiologists should have experience of a range of percutaneous valvular interventions, large-bore peripheral cannulation, and percutaneous suture closure. Cardiac surgeons should routinely perform complex open valvular procedures and be able to offer rescue or salvage surgery when complications arise. Bleeding from damaged peripheral vessels is not infrequent following TAVI, so it is also advantageous to also have onsite access to vascular surgeons and radiologists trained in either open or endovascular arterial repair.

4. Outcomes

Outcomes are events that are either present or absent in study participants at specific time points after an intervention or exposure. They can be clinical, patient-reported, healthcare economic, composite, or surrogate. Studies investigating outcomes of interventions for aortic valve pathology concentrate on the safety, feasibility, efficacy, and durability of treatment options. Safety is typically assessed with clinical measures, such as operative morbidity and mortality. Feasibility describes whether the procedure can be accomplished successfully without recourse to alternative treatment. Efficacy is defined as whether an intervention works in those who receive it. For aortic valve therapies, it is usually based on echocardiographic findings and functional outcomes, such as the New York Heart Association (NYHA) classification and HRQL tools. Durability includes long-term outcomes such as prosthesis failure, reoperation, and survival. High quality studies, including randomized controlled trials (RCTs), are required to evaluate these outcomes in patients with severe AS and to inform treatment choices between open AVR, TAVI, balloon valvuloplasty, and medical management. This section will summarize outcomes from studies that have investigated the use of TAVI.

4.1 Evidence from the PARTNER Trial

RCTs are the gold standard study design for assessing surgical innovation. However, there is a paucity of well-designed surgical RCTs, which is in part due to specific methodological difficulties. Surgery is a complex intervention and is comprised of multiple events that interact together to affect outcomes. For example, perioperative mortality may be affected by patient factors (e.g. comorbidities), surgeon factors (e.g. skill and technique), anesthetic factors (e.g. quality of postoperative care) and service factors (e.g. number of nursing staff, rehabilitation services). If these factors are poorly controlled in an RCT, then confounding variables may result in bias. It is important that trials clearly predefine all aspects of the intervention in the study protocol and report protocol deviations in subsequent publications. The timing of surgical RCTs is also critical. RCTs undertaken too early in the development of a novel intervention may underestimate treatment effect magnitude as a consequence of operator learning-curve effects. RCTs undertaken too late after the

introduction of a procedure can be unethical because of a loss of equipoise. It is difficult to blind participants and clinicians in surgical RCTs due to differences in outward appearances of wounds, and because the surgeon will always know which procedure has been performed. This problem can be overcome by blinding outcome assessors and data analysts to the allocation sequence. Another problem with surgical RCTs relates to the fact that they are often costly to undertake, and follow-up needs to be long-term to identify late and rare events.

The PARTNER Trial was the first RCT to compare outcomes between TAVI and other interventions for severe AS (Leon *et al.*, 2010). The study consisted of two parallel, prospective, multicenter, randomized trials. The first of these (Cohort A) randomized to either TAVI or open AVR participants with severe AS who were considered high-risk for surgery (STS-PROM > 10% mortality risk or > 15% predicted 30-day mortality). In Cohort B, patients with severe AS and considered unsuitable for surgery (> 50% predicted 30-day mortality or a serious irreversible condition) were allocated to either TAVI or medical management, which included balloon valvuloplasty. The primary outcome measure in Cohort A was survival at one year. In Cohort B, the primary endpoint was initially survival for the duration of the study, although this was supplemented partway through the trial with a composite co-primary outcome of survival and time to first rehospitalization. Secondary outcome measures included: functional improvement in NYHA classification; freedom from major adverse cardiovascular and cerebrovascular events (MACCE); evidence of prosthetic valve dysfunction (hemolysis, infection, thrombosis, severe paravalvular leak, or migration); a six-minute walk test; length of hospital stay; total hospital days from the index procedure to one year postoperatively; HRQL at 30 days, six months, and one year; improvement in aortic valve area; and a composite of survival, recurrent hospitalization, and NYHA class. The eligibility criteria for the PARTNER Trial are listed in Table 2.

To date only results from Cohort B have been published, with the findings of Cohort A expected in late 2011. Between May 2007 and March 2009, 358 consecutive patients with severe AS who were considered unsuitable for surgery (Cohort B) were enrolled at 21 centers. Randomization allocated 179 patients to receive TAVI (Edwards SAPIEN device using the transfemoral approach) and 179 to be treated with medical management. Participants were followed-up for at least one year. The rate of death from any cause at one year post-randomization (primary endpoint) was 30.7% in those treated with TAVI and 50.7% in those treated with medical care alone (hazard ratio: 0.55; 95% confidence interval: 0.40 to 0.76; $p < 0.001$). The cardiovascular mortality rate one year after randomization was also lower in the TAVI group (20.5% vs. 44.6%; hazard ratio: 0.39; 95% confidence interval: 0.27 to 0.56; $p < 0.001$). Furthermore, the composite endpoint of rate of death from any cause and rehospitalization at one year (co-primary endpoint) was 42.7% with TAVI compared with 71.6% with medical care alone (hazard ratio: 0.46; 95% confidence interval: 0.35 to 0.59; $p < 0.001$).

Complications were observed more frequently in the TAVI arm of the trial. There was a greater incidence of cerebrovascular events after TAVI at both 30 days after randomization (6.7% vs. 1.7%, $p = 0.03$) and at one year (10.6% vs. 4.5%, $p = 0.04$). Patients who received TAVI were also more likely to suffer major bleeding or vascular complications. Despite this, 30-day mortality was similar between groups. Patients treated with TAVI demonstrated marked improvements in functional outcomes: 74.8% of patients alive at one year in the TAVI arm were asymptomatic or had only mild symptoms (NYHA classes I or II), compared with 42.0% of surviving participants in the medical care alone group ($p < 0.001$). In addition,

Inclusion criteria for the PARTNER Trial:
<ul style="list-style-type: none"> • Patients must have comorbidities such that the surgeon and cardiologist Co-Principle Investigators concur that the predicted risk of operative mortality is $\geq 15\%$ and/ or a minimum STS-PROM score of 10. • Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area of < 0.8 cm². • Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater. • The patient or the patient's legal representative has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent as approved by the IRB of the respective clinical site. • The patient and the treating physician agree that the patient will return for all required post-procedure follow-up visits. <p>Cohort B All candidates for Cohort B in this study must meet #2, 3, 4, 5 of the above criteria and:</p> <ul style="list-style-type: none"> • The patient, after formal consults by a cardiologist and two cardiovascular surgeons, agrees that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%.
Exclusion Criteria for the PARTNER Trial:
<ul style="list-style-type: none"> • Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment (defined as Q wave MI, or non-Q wave MI with total CK elevation \geq twice normal in the presence of CK-MB elevation or troponin level elevation (WHO definition). • Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was noncalcified. • Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation $> 3+$). • Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation). • Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, or severe (greater than 3+) mitral regurgitation. • Blood dyscrasias as defined: leukopenia (WBC < 3000 mm³); acute anemia (Hb < 9 mg%); thrombocytopenia (platelet count $< 50,000$ cells/mm³); history of bleeding diathesis or coagulopathy. • Untreated clinically significant coronary artery disease requiring revascularization. • Hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices. • Need for emergency surgery for any reason. • Hypertrophic cardiomyopathy with or without obstruction. • Severe ventricular dysfunction with LVEF $< 20\%$. • Echocardiographic evidence of intracardiac mass, thrombus or vegetation. • Active peptic ulcer or upper gastrointestinal bleeding within the prior 3 months. • A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid),

<p>or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated.</p> <ul style="list-style-type: none">• Native aortic annulus size < 18 mm or > 25 mm as measured by echocardiogram.• Recent (within 6 months) cerebrovascular accident or transient ischemic attack.• Renal insufficiency (creatinine > 3.0 mg/dL) or end-stage renal disease requiring chronic dialysis.• Life expectancy < 12 months due to noncardiac comorbid conditions.• Significant abdominal or thoracic aorta disease, including aneurysm (defined as maximal luminal diameter 5 cm or greater), marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated), narrowing of the abdominal aorta (especially with calcification and surface irregularities), or severe “unfolding” and tortuosity of the thoracic aorta.• Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath, such as severe calcification, severe tortuosity or vessels size diameter < 7 mm for 22F sheath or < 8 mm for 24F sheath.
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Table 2. Eligibility criteria for participants included in the PARTNER Trial (Leon *et al.*, 2010)

there was a significant improvement in the six-minute walk test in patients treated with TAVI, but not in those who received medical care alone. Echocardiography demonstrated a significant reduction in aortic valve area and transvalvular gradient at 30 days in patients receiving TAVI. Moreover, these findings were maintained at one year, which suggested that TAVI devices are durable at least into the medium term.

Leon *et al.* (2010) concluded that medical care alone did not alter the course of severe AS in patients who were not candidates for surgery. Transfemoral TAVI was markedly superior to medical care alone in this high-risk cohort of patients, and TAVI improved the rates of all-cause and cardiovascular mortality. This is emphasized by the fact that only five patients needed to be treated with TAVI to prevent one death in the first year of follow-up. The safety of TAVI was highlighted by the similar 30-day mortality rate to medical care alone, despite a greater risk of vascular damage and bleeding, which were attributed to the large bore femoral access sheaths required in early versions of the Edwards SAPIEN heart-valve system. It is likely that future use of lower profile sheaths will reduce the incidence of vascular damage. Stroke rates were greater with TAVI and are the likely consequence of atherosclerotic emboli released during deployment of the valve. Less traumatic TAVI systems and novel cerebrovascular protection devices may help limit the incidence of stroke. It is noteworthy that increased survival was associated with improved function: patients treated with TAVI not only lived longer but also had fewer symptoms. Transfemoral TAVI is the current standard of care in patients who are not considered candidates for open AVR. The PARTNER Trial provides the best evidence yet to support the use of TAVI, although it is important to interpret the findings of Cohort B in the light of several limitations. The first of these relates to external validity: the PARTNER Trial was predominantly explanatory rather than pragmatic and had strict eligibility criteria (Table 2). Consequently, the results should not be extrapolated to patients with characteristics different from those enrolled in the trial, such as patients with peripheral vascular disease or severe LV dysfunction and those requiring coronary artery bypass grafts. Furthermore, the trial investigated only the transfemoral approach with a single device (Edwards SAPIEN), which has now been superseded by newer prostheses. Methodologically the trial is limited by poor reporting of randomization, allocation concealment, and blinding, while there is evidence of selective

reporting of outcomes and the introduction of a co-primary outcome during the conduct of the trial. One final observation is that the trial offers only limited information on the long-term durability of TAVI prostheses. Additional long-term randomized controlled trials are warranted, the results of which, together with the results of Cohort A, will offer some insight into the relative efficacy of TAVI and open AVR in high-risk patients.

Since the first report of TAVI almost a decade ago, there has been an explosion in the number of related publications. Most of these are retrospective case series or comparative studies contrasting different approaches (transapical vs. transfemoral) or devices (Medtronic CoreValve vs. Edwards SAPIEN). Although the publications do not provide the same level of evidence as RCTs and are open to selection and recall bias, it is worth considering their findings because of their number. The next section summarizes the support or otherwise for TAVI from nonrandomized studies in terms of feasibility, safety, efficacy, and durability.

4.2 Feasibility of TAVI

The feasibility of TAVI can be assessed by considering the procedural success rate, defined as whether the implant was successfully deployed without immediate complications or the need to convert to open surgery. Early reports of procedural success rates are likely to have been affected by operator learning-curve effects. Cribier *et al.* (2002) reported that, using the antegrade transvenous approach, 22 out of 26 implants (84.6%) were successfully deployed, with four failures due to technical complications. Failures occurred as a consequence of valve migration immediately after the procedure ($n = 2$) and poor tolerance of the guide wire across the mitral valve ($n = 2$). This high rate of technical achievement could not be replicated by other researchers using transvenous access due to the complexity of passing the guide wire through the interventricular septum and mitral valve.

The introduction of retrograde methods for accessing the diseased aortic valve has led to greater procedure reproducibility. Webb *et al.* (2007) initially reported outcomes for transfemoral TAVI using the Edwards prosthesis in 50 patients. The procedural success rate in this cohort was 86% (43 out of 50 patients), with failure associated with inability to pass the catheter through the iliac artery ($n = 1$) or across the aortic valve ($n = 3$), device malpositioning ($n = 2$), or malfunction of the delivery system ($n = 1$). Other authors have demonstrated similar success rates for the transfemoral approach using the Edwards Lifesciences devices. Rodes-Cabau *et al.* (2008) successfully implanted TAVI prostheses in 91% of their patients, with failure occurring as a result of severely calcified iliac disease ($n = 1$) and intra-operative death secondary to myocardial ischaemia ($n = 1$). Similarly, Descoutures *et al.* (2008) reported success in 10 out of 12 patients (83%). In this series, procedural failure was the consequence of an inability to cannulate the iliac vessels ($n = 1$) and of fatal hemopericardium due to left ventricular perforation by the guide wire ($n = 1$).

Only Edwards Lifesciences devices are currently licensed for use using the transapical approach. Ye *et al.* (2009) and Zierer *et al.* (2008) both reported success rates of 100% in small case series using transapical access. In larger studies the success rates are similarly impressive. In a study by Walther *et al.* (2008) successful implantation was accomplished in 47 out of 50 patients (94%), with three patients requiring conversion to open AVR. In another multicentre study by Walther *et al.*, 55 out of 59 implants were deployed successfully with four patients requiring urgent sternotomy and AVR due to device malposition (Walther *et al.*, 2007). In an article by Svensson *et al.* (2008), procedural success was 88% in 40 patients undergoing transapical TAVI. Of the five patients in whom TAVI was deemed to

have failed, the etiological factors were valve embolization (n = 3), valve migration (n = 1), and paravalvular leak (n = 1).

The Medtronic CoreValve system is licensed for use using only retrograde percutaneous methods, typically transfemoral. The feasibility outcomes for this device are excellent, with several studies reporting 100% success rates (Behan *et al.*, 2008; Berry *et al.*, 2007; De Jaegere *et al.*, 2008). In a large prospective registry of 646 patients by Piazza *et al.* (2008), the procedural success rate was 97%. The authors did not present reasons for failure of implantation of the CoreValve device. In a small study, Grube *et al.* (2006) achieved successful implantation of TAVI prostheses in 21 out of 25 patients (84%). Reasons for procedural failure included paravalvular leak (n = 2), inability to cross a heavily calcified aortic valve (n = 1), and sudden death during balloon valvuloplasty (n = 1). In a second multicenter study by Grube *et al.* (2007), the procedural success rate was comparatively low (74%), which appears to be the consequence of malpositioning of a significant number of implants. Tamburino *et al.* (2009) reported outcomes for 30 patients treated with CoreValve TAVI. The procedural success rate was 93%, with one incident of pericardial tamponade and one of malpositioning of the TAVI device necessitating VIV implantation. It can be concluded from these reports that TAVI is a feasible procedure and that success rates are likely to improve with greater operator experience and more advanced devices.

4.3 Safety of TAVI

The assessment of safety in cardiothoracic surgery is made through reporting 30-day major adverse cardiovascular and cerebrovascular events (MACCE). Thirty-day mortality is conventionally defined as the occurrence of death from any cause within 30 days of a procedure. However, definitions are sometimes heterogeneous and must be considered carefully when outcomes from multiple studies are combined. In the case of TAVI, 30-day mortality is generally favorable and ranges from 0% to 25% (Behan *et al.*, 2008; Berry *et al.*, 2007; Cribier *et al.*, 2002; De Jaegere *et al.*, 2008; Descoutures *et al.*, 2008; Grube *et al.*, 2006; Grube *et al.*, 2007; Piazza *et al.*, 2008; Rodes-Cabau *et al.*, 2008; Spargias *et al.*, 2008; Svensson *et al.*, 2008; Tamburino *et al.*, 2009; Walther *et al.*, 2007; Walther *et al.*, 2008; Webb *et al.*, 2007; Ye *et al.*, 2009; Zierer *et al.*, 2008). Thirty-day mortality rates appear to be similar between the different devices and between transapical and transfemoral access routes.

Vascular complications are one of the major concerns with percutaneous approaches. Vascular injury has been shown to occur in up to 18% of TAVI procedures and can lead to hemorrhage, limb ischemia, and amputation (Behan *et al.*, 2008; Descoutures *et al.*, 2008; Leon *et al.*, 2010; Piazza *et al.*, 2008; Rodes-Cabau *et al.*, 2008; Spargias *et al.*, 2008; Tamburino *et al.*, 2009; Thomas *et al.*, 2010; Webb *et al.*, 2007; Zierer *et al.*, 2008). The etiology of vascular damage is often attributed to the large-caliber sheaths used with early TAVI devices. It is envisaged that the introduction of low-profile introducers and greater operator experience will reduce vascular complications. In addition, percutaneous vessel closure devices for transfemoral access are now widely available and will contribute further to the reduction in periprocedural major hemorrhage. Onsite access to vascular surgeons and interventional radiologists with experience of open and endovascular repair of damaged vessels is encouraged. The team should be familiar with the use of crossover femoral cannulation, covered stents and balloon tamponade to control bleeding vessels.

Stroke and transient ischemic attacks (TIAs) are common sequelae of TAVI deployment (range: 0% to 10%) and are believed to be the consequence of atheromatous emboli from the

ascending aorta and diseased aortic valve (Berry *et al.*, 2007; Cribier *et al.*, 2002; Descoutures *et al.*, 2008; Grube *et al.*, 2006; Grube *et al.*, 2007; Leon *et al.*, 2010; Piazza *et al.*, 2008; Rodes-Cabau *et al.*, 2008; Svensson *et al.*, 2008; Tamburino *et al.*, 2009; Thomas *et al.*, 2010; Walther *et al.*, 2007; Webb *et al.*, 2007; Ye *et al.*, 2009; Zierer *et al.*, 2008). The risk of cerebrovascular events is increased in TAVI patients with atrial fibrillation and in those in whom valve thrombosis has occurred. Diffusion-weighted magnetic resonance imaging has demonstrated new cerebral lesions in up to 91% of patients undergoing TAVI (Ghanem *et al.*, 2010; Kahlert *et al.*, 2010). Fortunately, these radiological images do not correlate with clinically observed neurological deficits, which suggests that ischemic brain injury is predominantly subclinical (Lefevre *et al.*, 2011; Webb *et al.*, 2009a). The introduction of less traumatic delivery devices may help to reduce the incidence of cerebrovascular events, while novel catheters that are designed to capture or deflect emboli are under evaluation (Nietlispach *et al.*, 2010).

Occlusion of the left main coronary ostium is a potentially fatal complication of TAVI insertion. The usual mechanism involves upward displacement of the native aortic valve leaflet such that it completely covers the coronary ostia. Rarely, the device itself can abut against the coronary ostia, which reduces blood flow to the myocardium. Low coronary origin (less than 12 mm superior to the aortic annulus on computed tomography) or shallow coronary sinuses are thought to predispose to left main coronary artery occlusion (Tops *et al.*, 2008; Webb, 2009b). The Medtronic CoreValve has a tampered proximal end, which is designed to prevent coronary occlusion.

Bradycardia requiring a permanent pacemaker is a frequent problem following TAVI. It results from pressure effects on the conduction pathways that pass through the membranous interventricular septum beneath the aortic valve. This is particularly common in patients with a pre-existing bundle branch or atrioventricular block. Several additional factors are believed to predispose to pacemaker insertion: advanced age, oversizing of the implant, and the depth of the implant within the LV outflow tract (Willson & Webb, 2011). The Medtronic CoreValve is considerably longer than the Edwards SAPIEN and is in contact with a larger area of the interventricular septum. The CoreValve device is associated with considerably higher rates of pacemaker insertion (range: 20% to 38%) (Elchaninoff *et al.*, 2011; Jilaihawi *et al.*, 2010; Piazza *et al.*, 2010; Zahn *et al.*, 2011) compared to the Edwards SAPIEN (range 3% to 10%) (Elchaninoff *et al.*, 2011; Thomas *et al.*, 2010; Webb *et al.*, 2009a).

Although valvular aortic regurgitation is rare after TAVI, paravalvular leak occurs more commonly and is moderate or severe in up to 15% of patients (Leon *et al.*, 2010; Sherif *et al.*, 2010; Webb *et al.*, 2009a; Zahn *et al.*, 2011). Leak occurs when there is an inadequate seal between the outer surface of the device and the aortic annulus, which allows blood to flow around the periphery of the prosthesis. This may occur if the implant is deployed either too proximally or too distally in relation to the plane of the aortic annulus; when the chosen device is undersized in relation to the aortic annulus; or if the prosthesis fails to expand completely. Acute paravalvular leak can be treated with balloon valvuloplasty, retrieval of the device (if possible), or VIV techniques. TAVI has been shown to be associated with a higher incidence of paravalvular leak than open AVR (12% vs. 1%) (Leon *et al.*, 2010).

Acute renal impairment, defined as a glomerular filtration rate reduction of greater than 25%, is associated with a four-fold increase in 30-day mortality following TAVI (Willson & Webb, 2011). Acute renal impairment and renal replacement therapy occur in 11% and 1.4% of TAVI patients, respectively, with risk factors including chronic kidney disease, blood

transfusion, hypertension, chronic obstructive pulmonary disease, and transapical access (Bagur *et al.*, 2010). In patients with chronic kidney disease, the incidence of acute renal impairment is lower in those treated with TAVI than with open AVR (9% vs. 26%, $p < 0.001$) (Bagur *et al.*, 2010), which perhaps reflects the deleterious effects of cardiopulmonary bypass, hypotension, and ischemia associated with open surgery. TAVI may therefore be a safer therapeutic option for AS patients with a history of chronic renal impairment.

Open AVR in the presence of severe LV dysfunction is high-risk, and TAVI may be an appropriate alternative in this situation. A recent nonrandomized study (Clavel *et al.*, 2010) compared TAVI ($n = 83$) to open AVR ($n = 200$). Despite a higher STS-PROM score in patients who received TAVI, the authors reported that TAVI was associated with a greater improvement in ejection fraction than open AVR (14% vs. 7%; $p < 0.001$) and better hemodynamics at one year. Evidence from randomized trials is required to assess whether TAVI results in better recovery of LV function than does AVR.

Other complications associated with TAVI include: supraventricular tachyarrhythmia (range: 5% to 31%); ventricular tachyarrhythmia (range: 0% to 4%); myocardial infarction (range: 0% to 15%); cardiac tamponade (range: 2% to 10%); conversion to open surgery (range: 0% to 8%); conversion to valvuloplasty (range: 0% to 4%); emergency valve-in-valve procedure (range: 2% to 12%); and aortic dissection or rupture (range: 0% to 4%) (Behan *et al.*, 2008; Berry *et al.*, 2007; Cribier *et al.*, 2002; De Jaegere *et al.*, 2008; Descoutures *et al.*, 2008; Grube *et al.*, 2006; Grube *et al.*, 2007; Piazza *et al.*, 2008; Rodes-Cabau *et al.*, 2008; Spargias *et al.*, 2008; Svensson *et al.*, 2008; Tamburino *et al.*, 2009; Walther *et al.*, 2007; Walther *et al.*, 2008; Webb *et al.*, 2007; Ye *et al.*, 2009; Zierer *et al.*, 2008). The overall 30-day MACCE ranges from 3% to 35% (Behan *et al.*, 2008; Berry *et al.*, 2007; Cribier *et al.*, 2002; De Jaegere *et al.*, 2008; Descoutures *et al.*, 2008; Grube *et al.*, 2006; Grube *et al.*, 2007; Piazza *et al.*, 2008; Rodes-Cabau *et al.*, 2008; Spargias *et al.*, 2008; Svensson *et al.*, 2008; Tamburino *et al.*, 2009; Walther *et al.*, 2007; Walther *et al.*, 2008; Webb *et al.*, 2007; Ye *et al.*, 2009; Zierer *et al.*, 2008).

4.4 Efficacy of TAVI

The efficacy of valvular procedures can be determined by whether they improve echocardiographic measurements of hemodynamic performance and by the effect of treatment on patient function and quality of life. The main pathological findings at echocardiography in patients with severe AS are reduced AVA, raised peak and mean pressure gradients across the aortic valve, reduced LV ejection fraction, and LV dysfunction. Numerous studies have investigated the echocardiographic outcomes of TAVI and have consistently demonstrated statistically significant ($p < 0.05$) improvements in AVA, mean and peak aortic valve pressure gradients, and LV ejection fraction between preoperative and early postoperative values (Behan *et al.*, 2008; Berry *et al.*, 2007; Clavel *et al.*, 2009; Cribier *et al.*, 2002; De Jaegere *et al.*, 2008; Descoutures *et al.*, 2008; Figulla *et al.*, 2011; Grube *et al.*, 2006; Grube *et al.*, 2007; Piazza *et al.*, 2008; Rodes-Cabau *et al.*, 2008; Spargias *et al.*, 2008; Svensson *et al.*, 2008; Tamburino *et al.*, 2009; Walther *et al.*, 2007; Walther *et al.*, 2008; Webb *et al.*, 2007; Ye *et al.*, 2009; Zierer *et al.*, 2008). Furthermore, there is no deterioration in echocardiographic outcomes in patients followed-up for at least a year, which suggests that TAVI produces longer-lasting effects than balloon valvuloplasty alone (Cribier *et al.*, 2002; Figulla *et al.*, 2011; Webb *et al.*, 2007; Ye *et al.*, 2009).

It is imperative that improvements in hemodynamics translate into tangible benefits to patient function and health status. In studies of cardiothoracic surgery, patient function and

the severity of symptoms are most commonly assessed through changes in NYHA classification. This clinician-reported outcome assigns patients to one of four categories, ranging from no symptoms or limitations on ordinary physical activity (Class I) to severe symptoms at rest necessitating continuous bed rest (Class IV). TAVI has been shown consistently to improve NYHA classification, with between 50% and 100% of patients demonstrating an improvement of at least one grade in NYHA classification at one-month post-procedure (Cribier *et al.*, 2002; Gotzmann *et al.*, 2010; Grube *et al.*, 2006; Grube *et al.*, 2007; Rodes-Cabau *et al.*, 2008; Spargias *et al.*, 2008; Svensson *et al.*, 2008; Webb *et al.*, 2007; Ye *et al.*, 2009). The short duration of follow-up of most studies means that it is difficult to determine whether these benefits are sustained, but some publications have reported that functional improvements last at least a year (Leon *et al.*, 2010; Webb *et al.*, 2009a). NYHA classification is also correlated with performance in the 6-minute walk test (Demers *et al.*, 2001; Gotzmann *et al.*, 2010).

Patient-reported outcomes (PROs), including health-related quality of life, provide unbiased assessments of health status from the patient's perspective. Instruments (most often questionnaires) designed to capture these issues are called HRQL tools and are multidimensional, encompassing perceptions of physical, emotional, and social function, as well as assessing specific symptoms caused by the disease and treatment (Fayers & Hays., 2005). The development of symptoms of congestive cardiac failure confers a poor prognosis on patients with severe AS and is likely to significantly affect HRQL. It is important to determine whether TAVI has a beneficial effect on HRQL and symptom palliation, in addition to increasing survival. Several studies have reported HRQL outcomes in patients treated with TAVI. Gotzmann *et al.*, (2010) reported that HRQL (assessed using the Minnesota Living with Heart Failure Questionnaire [MLHFQ]) was significantly better 30 days after TAVI when compared to baseline. This correlated with observed improvements in the 6-minute walk test and a reduction in serum beta-natriuretic peptide. Krane *et al.* (2010) measured HRQL with the Medical Outcomes Study Short Form-36 (SF-36) in a cohort of 99 patients treated with TAVI. Physical functioning, bodily pain, general health, and vitality all improved significantly from baseline at the three-month follow-up. Scores for social functioning and mental health remained static, while only role-emotional functioning deteriorated after TAVI. Ussia *et al.* (2009) used the SF-12 to compare HRQL in patients before and after TAVI with aged matched population reference values. Preprocedural AS patients had markedly worse HRQL than the general population for both physical and mental function. Five months after TAVI, HRQL had improved dramatically and was similar to that in the general population. This suggests that recovery following TAVI does occur, but takes several months. In the REVIVAL II feasibility study, HRQL was measured using the SF-12 and the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 30 days and 6 months after TAVI insertion in 75 patients (Reynolds *et al.*, 2008). At 30 days, a significant improvement in KCCQ score was observed, but not in the physical or mental functioning scales of the SF-12. However, by the 6-month follow-up, improvements in all facets of HRQL were evident. Taken together, these results provide strong evidence that TAVI improves HRQL in patients with severe AS, although it takes up to 6 months for HRQL to match that in the general population.

4.5 Durability of TAVI

TAVI is a relatively new intervention, and long-term outcome data is scarce beyond one year of follow-up. A recent systematic review (Figulla *et al.*, 2011) incorporating pooled data

from multiple studies reported that mean one-year survival after TAVI was 75.9% (range: 64.1% to 87.0%) (Al-Attar *et al.*, 2009; Grube *et al.*, 2008; Himbert *et al.*, 2009; Kapadia *et al.*, 2009; Otten *et al.*, 2009; Rajani *et al.*, 2010; Rodes-Cabau *et al.*, 2010; Thielmann *et al.*, 2009; Walther *et al.*, 2010; Webb *et al.*, 2009a; Ye *et al.*, 2009). In contrast the mean one-year survival rate for patients treated with medical care alone was 62.4% (range: 40.0% to 84.8%; $p < 0.01$ vs. TAVI), revealing a 13.5% survival advantage in favor of TAVI at one year. This is in agreement with the PARTNER Trial, which reported a 20% survival advantage for TAVI (Leon *et al.*, 2010). Gurvitch *et al.* (2010) are one of the few groups to report outcomes for TAVI beyond one year of follow-up: In a cohort of 70 patients undergoing TAVI, they reported one-, two-, and three-year survival rates of 81%, 74%, and 61%, respectively, although patients who died within 30-days or in whom TAVI failed were excluded from the analysis. During the follow-up period, there were 30 late deaths, of which three were valve-related: two patients died from intracerebral hemorrhage secondary to supratherapeutic anticoagulation, and sudden death occurred in another patient who was found postmortem to have an overgrowth of fibrous connective tissue around the prosthesis. No deaths were directly related to valvular dysfunction, which is in agreement with other studies reporting outcomes up to one year (Grube *et al.*, 2008; Rodes-Cabau, 2010; Webb *et al.*, 2009a). In the review by Figulla *et al.* (2011), one-year survival following transfemoral TAVI (79.2%, range: 68.1% to 87.0%) was superior to transapical access (73.6%, range 60.0% to 78.0%, $p = 0.04$). Reduced survival in patients receiving transapical TAVI may be explained by the need for general anesthesia, thoracotomy, and cannulation of the left ventricular apex. It is important to note that most studies included in Figulla *et al.* were retrospective and nonrandomized, and consequently at risk of bias. RCTs are required to determine which method of gaining access to the diseased aortic valve is the most efficacious when undertaking TAVI.

Very little is known about the risk of valvular degeneration with TAVI devices. *In vitro* testing of the latest generation of Edwards SAPIEN/XT and Medtronic CoreValve devices suggests that durability in excess of 10 years can be expected (Willson & Webb., 2010). Because of the proven efficacy of open AVR, without long-term *in vivo* data, it is very unlikely that TAVI devices will be licensed for use in younger patients without comorbidities. Indeed, freedom from reoperation for valvular degeneration is greater than 95% with modern surgical bioprostheses (Jamieson *et al.*, 1995). The results of long-term follow-up will be required to answer this clinical question, but it is unlikely that TAVI will replace open AVR for the management of uncomplicated, severe AS.

5. Future directions

The evidence base for TAVI is rapidly evolving, and there has been a significant rise in the number of new publications over the last five years. Most eagerly awaited are the findings of Cohort A of the PARTNER Trial. This will provide insight into the comparative efficacy of TAVI and open AVR in high-risk patients with severe symptomatic AS. The results of this trial will have important implications for healthcare policy implementation and may mean greater financial provision for TAVI in high-risk patients. In addition, the two main techniques for accessing the aortic valve (transfemoral and transapical) will need to be compared in an RCT, especially given that pooled data suggests one-year survival is worse after transapical TAVI (Figulla *et al.*, 2011). If this is proved to be the case, then the transapical approach may be restricted to patients in whom the transfemoral route is contraindicated.

Using TAVI in moderate- or low-risk patients is not currently justified, because it would be unethical to withhold access to open AVR with its proven efficacy. The results of long-term follow-ups (> 10 years) of high-risk patients will be necessary to assess the durability of TAVI implants and to inform decisions about their use in younger, fitter patients. Given the short life expectancy of patients denied open surgery, it is unlikely that sufficient data will be available in the foreseeable future to determine whether TAVI is appropriate in low-risk candidates. It is also worth noting that a number of new prostheses will undoubtedly emerge in the next decade and that they will require appropriate evaluation against existing gold standards. An RCT using the Medtronic CoreValve system is also anticipated to publish its findings in 2013. Once the feasibility, safety, efficacy, and durability of TAVI devices have been established, the onus will shift towards healthcare economic evaluation to identify the most cost-effective means of treating severe AS. It is certainly conceivable that minimally invasive techniques, such as TAVI, will prove cost-effective in the long-term.

6. Conclusions

Severe aortic stenosis has a poor prognosis once symptoms of congestive cardiac failure and angina develop. It is conventional wisdom that surgical AVR offers the best hope of symptom palliation and long-term survival. However, approximately one-third of patients with severe symptomatic AS are denied access to surgery because of comorbidities and high operative risk. The last decade has witnessed the introduction of transcatheter aortic valve implantation, a surgical innovation that permits percutaneous replacement of the diseased aortic valve without sternotomy and a cardiopulmonary bypass. TAVI remains in its infancy, yet it has demonstrated superior medium-term survival, fewer symptoms, and a better quality of life than medical care alone. Doubts persist over the durability of the implants, long-term outcomes, and the relative efficacy compared with surgical AVR in high-risk patients. However, TAVI is set to continue to revolutionize the management of severe symptomatic aortic stenosis.

7. References

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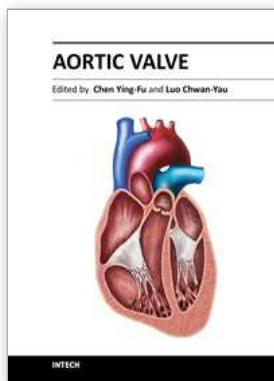
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Much has evolved in the field of aortic valve disease because of the increase in knowledge in the last decade, especially in the area of its management. This book "Aortic Valve" is comprised of 18 chapters covering basic science, general consideration of aortic valve disease, infective endocarditis, aortic sclerosis and aortic stenosis, bioprosthetic valve, transcatheter aortic valve implantation and a special section on congenital anomalies of the aortic valve. We hope this book will be particularly useful to cardiologists and cardiovascular surgeons and trainees. We also believe that this book will be a valuable resource for radiologists, pathologists, cardiovascular anesthesiologists, and other healthcare professionals who have a special interest in treating patients with aortic valve disease. We are certain that information in this book will help to provide virtually most new areas of aortic valve disease that will be employed in the current era.

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