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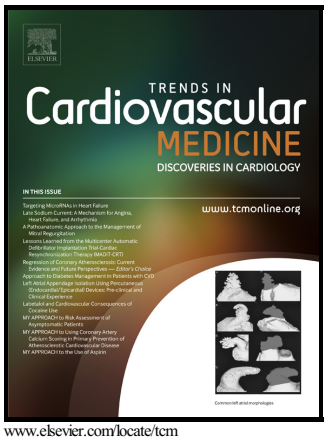

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Long term outlook for transcatheter aortic valve replacement

Andras P. Durko MD, Ruben L. Osnabrugge MD PhD, A. Pieter Kappetein MD PhD

Department of Cardio-Thoracic Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands

Corresponding author:

Andras Peter Durko MD

a.durko@erasmusmc.nl

Thoraxcentrum

Erasmus MC - University Medical Center Rotterdam

s'-Gravendijkwal 230

3015CE Rotterdam Nederland

ABSTRACT

Transcatheter aortic valve replacement (TAVR) revolutionized the treatment of severe symptomatic aortic stenosis (AS). TAVR is increasingly offered for lower-risk patients. The role and place of TAVR in the future treatment of AS is not clear yet. In this review, we discuss the long term outlook for TAVR, its challenges and its relationship to conventional surgical aortic valve replacement.

Introduction

Aortic stenosis. Parallel to the ageing of the western population, degenerative valvular diseases, and particularly aortic valve stenosis (AS), are becoming increasingly prevalent, imposing a significant social and economic burden on the society (1, 2). Besides impairing quality of life, severe symptomatic AS ultimately leads to death within a relatively short period of time if not treated with valve replacement (3). In this light, the fact that severe symptomatic AS was historically under-treated and AS is even under-diagnosed is particularly striking (4, 5). The reasons lie in the common belief that some patients with "high-risk" features would not profit from surgical aortic valve replacement (SAVR) or simply will not survive the stress associated with the operation: the perceived risk of the procedure was deemed to be "prohibitive".

Concept of TAVR. The concept of transcatheter aortic valve replacement (TAVR) involves deploying a stent-mounted bioprosthetic valve in the aortic position, utilizing exclusively transvascular access with the avoidance of sternotomy and cardiopulmonary bypass. The procedure can be performed in a cath lab using fluoroscopy and echocardiographic guidance. In contrast to the traditional surgical approach when the diseased valve is excised, during TAVR the native aortic valve is compressed between the stent frame and the aortic wall.

The idea of percutaneous valve implantation dates back to the late 1980s, and is based on the pioneering work of Henning Rud Andersen, Philipp Bonhoeffer and Alain Cribier (6-8). Due to the fear of procedural complications, the concept of TAVR met limited initial enthusiasm: some even termed the idea as the "the most stupid I've ever heard" (9).

The current role of TAVR in clinical practice. However, following the first successful first-in-human implant, TAVR revolutionized the treatment of severe AS in only over a decade. Firstly, randomized-controlled trials proved the superiority of TAVR over medical therapy

and over SAVR in patients having prohibitive or high surgical risk (10-13). These data formed the basis of guideline recommendations for TAVR in these risk categories, only a few years after its initial clinical introduction (14, 15). Consequently, TAVR numbers saw a dramatic increase year-by-year, and in some countries with unrestricted TAVR availability, the annual number of patients treated for severe AS has been effectively doubled over the past decade (16, 17). Recently, evidence supporting the use of TAVR in intermediate-risk patients has been established (see Table 1) (18, 19).

Prosthesis design, access routes and procedural improvements

Evolution of valve design. Based on primary design, two distinct groups of TAVR valves can be identified: they are either (i) "balloon-inflatable", as the original Cribier-Edwards valve and later the SAPIEN (Edwards Lifesciences, Irvine, California, US) valve family; or are (ii) "self-expandable" as the CoreValve (Medtronic, Minneapolis, Minnesota, US) and its successors. The initial concept was the "balloon-inflatable" valve: a prosthetic valve inside a metal stent, crimped and mounted on a balloon. To deploy the valve, the balloon must be inflated. Quickly following the introduction of the first "balloon-expandable" valves, the idea of utilizing "self-expandable" stents not requiring ballooning emerged. This concept makes use of the unique properties of nitinol (nickel-titanium alloy): malleable at lower temperatures, a nitinol stent regains its original conformation and radial strength at normal body temperature.

Future design directions. The main directions of future design development are (i) to decrease the delivery profile (i.e. making the crimped valve thinner), therefore making smaller vessels eligible for vascular access, while maintaining the stent's radial strength; and (ii) to decrease the likelihood of paravalvular regurgitation. These can be achieved by modifying either the size or shape of the stent cells, and extending the sealing skirt or adding additional

outer sealing to the prosthesis. The third main focus point is to construct a repositionable and retrievable valve. To date, almost all available prostheses have this ability, although some are reported to suffer from engineering problems necessitating further modifications (20).

Besides the stent-mounted prostheses, a unique and promising concept was the Direct Flow (Direct Flow Medical, Santa Rosa, California, US) valve, utilizing a completely non-metallic design. The hollow plastic frame suspending the valve had to be filled with a solidifying polymer to permanently fix the prosthesis in the desired position. Unfortunately, despite the promising initial results, the company had to cease its activities due to lack of financial support and the valve is not available on the market (21).

Alternative vascular access. The first human implant was performed through the femoral vein with transseptal puncture, anterograde aortic valve crossing and deployment (8). Soon the more straightforward retrograde approach through the femoral artery gained popularity, and became the "gold standard" in clinical practice. However, as some patients have tortuous, calcified or simply too narrow ilio-femoral vasculature rendering them unsuitable for transfemoral-TAVR (TF-TAVR), the need for an alternative vascular access route is evident.

Initially, the anterograde transapical approach (TA-TAVR) seemed to be an attractive alternative. Later it became obvious that TA-TAVR is associated with an increased risk of bleeding, myocardial injury, pulmonary complications and an overall higher risk of post-procedural mortality when compared to TF-TAVR (22, 23). Reasons are not perfectly clear and might be attributable to the more invasive procedure involving a thoracic incision, to the pre-selection of patients (as TA-TAVR is only considered if TF-TAVR is not feasible), or to the combination of both.

Nevertheless, the search continued: the possibility of using the subclavian or axillary artery, the ascending aorta, or the carotid artery as an alternative to TF-TAVR had been extensively

investigated in the past years. Results from the ROUTE registry demonstrate promising results with the direct transaortic approach; however this involves a partial sternotomy or a mini-thoracotomy (24). Trans-axillary or trans-subclavian TAVR usually requires a surgical cut-down, although successful percutaneous cases have been reported (25, 26). Similarly, trans-carotid access can be performed safely, even under local anesthesia alone (27).

An interesting new concept, the trans-caval access with abdominal aortic puncture and retrograde valve deployment emerged recently. This approach demonstrated safety and efficacy in a relatively large (n=100) series of patients unsuitable for both transfemoral and transthoracic valve delivery, and may gain further acceptance in the future (28).

Despite all of these efforts, the "second best" vascular access route for TAVR is yet to be identified. If an alternative access route is needed, this should be determined on a patient-by-patient basis.

Procedural improvements. Parallel to the continuous device development, several procedural changes have been implemented to further improve TAVR outcomes and decrease the burden associated with the procedure. The principal objectives are to perform the procedure (i) under local anesthesia and (ii) totally percutaneously. Avoiding general anesthesia during TAVR yields better outcomes and reduces the length of in-hospital stay (29). However, this approach precludes the routine use of intra-procedural transesophageal echocardiography. Therefore, advanced transthoracic echocardiography monitoring or additional non-imaging methods are necessary to assess post-procedural aortic regurgitation (30). The use of low-profile or balloon-expandable sheaths and advanced vascular closure devices can facilitate totally percutaneous TF-TAVR, thereby promoting early mobilization.

TAVR for everybody? Complications and cost-effectiveness

Although being less invasive, TAVR is not a procedure without risks and complications (Table 2., Table 3.), and in many aspects does not yield better outcomes when compared to SAVR. Despite its overall success, several TAVR-related issues are yet to be solved.

Paravalvular regurgitation. While post-procedural aortic regurgitation (AR) is traditionally an unacceptable finding following SAVR, roughly 25% of all patients after TAVR have mild-or-more, mostly paravalvular AR (31). The main underlying reason is that the diseased, often severely calcified native valve and annulus create an uneven surface for valve deployment. Although only moderate-to-severe AR is associated with increased early and late mortality and the reported incidence is decreasing over the past years, moderate-to-severe AR can still be expected around 5% following TAVR, ten times more frequently than after SAVR (19, 32). The consequences of post-procedural AR are especially important in younger patients, and necessitate further procedural and device development.

Permanent pacemaker need after TAVR. Due to the proximity of the electrical conduction system of the heart to the aortic annulus, rhythm disturbances can occur after aortic valve replacement, often necessitating permanent pacemaker implantation. Permanent pacemaker need after SAVR was around 5% in a large US database, while it is around 10% following TAVR according to the TVT registry report (33, 34). Balloon-expandable designs are associated with lower pacemaker rates when compared to self-expandable ones (18, 19). In a recently developed model, pre-procedural right bundle branch block, shorter membranous septum and noncoronary cusp device-landing zone calcium volume were identified as predictors of pacemaker need after TAVR with a third-generation balloon-expandable prosthesis (35). Of note, pacemaker requirement after TAVR also varies between different valve generations, and is influenced by the technique of implantation (36).

Neurological complications. Aortic valve interventions are associated with increased risk of cerebrovascular events. After contemporary SAVR, stroke occurs in 1.5% of patients, while the stroke rate following TAVR was 2% in the latest report from the Transcatheter Valve Therapy (TVT) registry (31, 37). To overcome the risk of cerebral embolism, several intravascular embolic protection devices had been developed in the past years. Although these devices are reported to capture embolic debris in 99% of all cases and are clearly beneficial from a logical viewpoint, proving their efficacy is not as straightforward statistically (38, 39). One of these filters, after obtaining CE mark several years ago, received FDA approval only recently (40).

Besides manifest stroke, subclinical cerebral microembolization is another TAVR-related issue. Although more common after TAVR, cerebral microembolization seems to have no effect on early or mid-term health-related quality-of-life (41). However, the long-term effects on cognitive function are unknown and should be further investigated.

Subclinical valve thrombosis. Another TAVR-related question to be answered is the frequency and clinical impact of subclinical leaflet thrombosis. Traditionally, bioprosthetic heart valve thrombosis was believed to be rare. The problem gained wider attention during the PORTICO IDE trial (St. Jude Medical, Saint Paul, Minnesota, US): post-procedural CT revealed a strikingly high incidence of leaflet thickening and reduced motion, a finding often missed by transthoracic echocardiography. Since then, subclinical valve thrombosis was reported in various transcatheter and surgical valves. Lack of post-procedural warfarin treatment and larger prosthesis size were identified as predictors (42). Further investigations linked the phenomenon to post-procedural neurological events and even to the suspicion of accelerated prosthesis degeneration (42, 43). Of note, most cases were reversible by initiating oral anticoagulants. However, as the clinical significance is not clarified yet, further

investigations are warranted before revising the recommendations on the optimal anticoagulation strategy following TAVR.

Vascular and access site related complications. Major vascular complications following TAVR include iatrogenic aortic dissection or annular rupture, and access site-related vascular injury leading to major bleeding (44). Although having completely different clinical impact, these are frequently reported as a combined endpoint in clinical trials (11, 13, 18, 19). Access site related major vascular complication rates following TAVR are around 1% according to the latest report from the TVT registry (34). Suture-based percutaneous vascular closure devices and balloon-expandable sheaths are expected to decrease the incidence of access site related complications.

Cost-effectiveness. Besides clinical outcomes, costs and cost-benefit ratios can be important factors when choosing a treatment modality, especially in countries with lower healthcare budgets. SAVR is associated with different costs when stratified by surgical risk category: the higher the predicted risk, the higher the costs that can be expected and vice-versa (45). Therefore, although the benefits of TAVR come at an economically acceptable cost in the higher-risk groups, this might not be true for lower-risk patients (46, 47). Finally, the expected changes in the price of TAVR prostheses can be fundamental influencers of cost-effectiveness when comparing TAVR versus SAVR.

TAVR for the young?

Initially, TAVR was an option reserved mainly for the elderly. Recently, a continuous decrease in the "age limit" is observed in clinical practice (17, 34). Of note, clinico-anatomical characteristics of AS might be different in the lower age group (48). Additionally, questions regarding long-term prosthesis durability must be answered before routinely offering TAVR for younger patients.

Bicuspid aortic valves. As bicuspid aortic valves are more prevalent in younger AS patients, the feasibility of TAVR in bicuspid AS is of particular importance when decreasing the age limit for TAVR (48-50). In contrast to tricuspid valves, bicuspid aortic valves tend to exhibit more eccentric and heavy calcification, and TAVR with early-generation devices was associated with more frequent aortic root injury and paravalvular AR in bicuspid AS patients (51). Notably, complication rates are reported to decrease with the introduction of newer devices (51). Further increasing the safety of TAVR in bicuspid AS is an important target of future device development.

Questions regarding durability. Over the past decade, bioprosthetic heart valves became increasingly popular in all age groups because of the possibility to avoid long-term anticoagulation (37). Surgical bioprostheses, however, are known to have limited long-term durability, although some have demonstrated excellent outcomes even after 20 years following implantation. Of note, a lower age at surgery is associated with impaired long-term results (52).

As TAVR was introduced into clinical practice only a decade ago, data on durability are still in accumulation. Initial reports on mid-term, 5-year results are encouraging: transvalvular gradients and the degree of aortic regurgitation remained stable when compared to the immediate post-procedural data (53-56). Of note, as until recently TAVR was reserved for elderly high-risk patients, the majority died before they could "outlive" their prosthesis. Thus, only a small percentage of the original cohorts was alive and available for the freedom from structural valve deterioration analyses at five years: less than 20% (86/519) of the original cohort in the PARTNER I trial (54). As a result, drawing firm conclusions from the currently available data on long-term durability is difficult.

Additionally, catheter mounted prostheses must be folded – a process called "crimping" – when assembling the delivery system. This procedure can potentially damage the leaflets, adversely affecting prosthesis' longevity – however this hypothesis is yet to be confirmed.

Valve-in-valve TAVR. In case of bioprosthetic valve failure, implanting a second transcatheter valve into the failing prosthesis seems to be an attractive option. Valve-in-valve (ViV) procedures have been carried out successfully in various clinical scenarios: from treating degenerated aortic bioprostheses to implanting transcatheter valves into surgical mitral annuloplasty rings (57). Naturally. however, implanting a second valve within the frame of the previous one creates a smaller orifice and consequently ViV-TAVR yields increased post-procedural gradients (58). A lesson learned from experience with surgical bioprostheses is that increased post-operative gradients and prosthesis-patient mismatch (PPM) adversely affect long-term durability: an association that is even more pronounced in younger patients (52). Therefore, treating a failing bioprostheses with ViV-TAVR in a young individual may create a vicious circle of increased gradients, PPM, rapid prosthesis degeneration and re-interventions. As a conclusion, ViV-TAVR may be a good option for the elderly, but is not an optimal solution for the problem of bioprosthesis failure in younger patients.

Bioengineered heart valves. Constructing living heart valves from cell-free, synthetic, bioresorbable scaffolds with *in situ* tissue engineering can play a role in overcoming limited bioprosthesis durability. Recently, these valves demonstrated promising early (12 months) results in the pulmonary position in vivo (59, 60). However, extensive product development is necessary until off-the-shelf bioengineered transcatheter heart valves might become available in the future.

Role of the Heart Team

A successful TAVR program requires a strong multidisciplinary approach. At least an interventional cardiologist, a cardiac surgeon and preferably a specialist of cardiovascular imaging as well as a geriatrician should be involved in the shared decision-making process to optimize treatment allocation. Performing unnecessary procedures should be prevented when invasive treatment is considered futile. The preoperative evaluation should comprise not only traditional risk factors, but also more elusive factors including frailty (61). Development and use of dedicated TAVR risk-scores complete the multidisciplinary decision-making (62, 63).

Who should perform TAVR?

Achieving and maintaining proficiency in an invasive procedure requires practice. To ensure patient safety, defining a minimum required annual case load for centers and for individual operators is justified. However, no clear-cut minimum TAVR volume requirements have been identified so far (64-66). According to expert consensus, performing TAVR is recommended only at centers with on-site cardiac surgical facilities (14, 66). However, a debated issue is the extent of surgical involvement during the procedure. Two strongly opposing opinions exist: some are even questioning the necessity of surgical backup, claiming similar outcomes in centers with and without on-site cardiac surgery in registry data (67). On the contrary, some are advocating for more active surgical involvement in the procedure and suggest the active "re-training" of surgeons in catheter-based techniques and "wire skills". A recent Society of Thoracic Surgeons survey reported a high degree of active surgical involvement in performing TAVR in the US (68). Although the finding was greeted and encouraged by the Society, the debate on the magnitude of surgical involvement in performing TAVR will continue.

Standardized outcome reporting

Many issues regarding TAVR warrant further investigations. However, if different studies would investigate and report different outcomes, comparing and summarizing their results would be difficult. Therefore, the use of universal definitions in outcome reporting is of paramount importance. The first "Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials" consensus document was published by the Valve Academic Research Consortium (VARC) in 2011, defining a wide range of procedure- and prosthesis-related endpoints. The document was last updated in 2012 and is used extensively both in randomized clinical trials and registries (44).

Future outlook

In recent years, TAVR rapidly evolved from a bail-out therapy to become an established treatment of AS in high-risk patients. Furthermore, the non-inferiority of TAVR over SAVR in intermediate-risk patients is also proven (Table 1.) and incorporated into the latest guideline recommendations (18, 19, 69). Of note, the vast majority of SAVR patients are in the low-risk category (37). As ongoing randomized-controlled trials are already investigating TAVR in low-risk patients (clinicaltrials.gov identifiers: NCT02675114, NCT02825134 and NCT02701283), results favoring TAVR over SAVR in this risk stratum may fundamentally change current clinical practice (Table 4.).

Still, in some areas TAVR currently yields worse outcomes when compared to SAVR. A ten-times more frequent paravalvular AR, associated with a proven negative effect on survival, or the unclear long-term durability may be justified in high-risk patients, but might preclude recommending TAVR in low-risk patients. These issues remain, even if the low-risk trial results would favor TAVR over SAVR at 1 or 2 years of follow-up. Only high-quality long-term follow-up in these trials can give us the definitive answer on the optimal treatment strategy in low-risk patients. The role of professional societies and the Heart Team will be

even more prominent in the future, when translating these trial results into everyday clinical practice.

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Table 1. Primary results of landmark TAVR trials in severe AS

Trial	Mean patient age [years]	Total number of patients (TAVR / SAVR)	Risk category	Mean STS-PROM	TAVR device	Primary endpoint	Time frame for primary endpoint	Conclusion
PARTNER 1 Cohort B (10)	83	358 (179/179)*	Extreme	11.5	SAPIEN	Death	1 year post-procedure	TAVR is superior over medical therapy in prohibitive surgical risk
PARTNER 1 Cohort A (11)	84	699 (348/351)	High	12	SAPIEN	Death	1 year post-procedure	TAVR is non-inferior to SAVR in high surgical risk
Medtronic CoreValve® U.S. Pivotal Trial (13)	83	747 (390/357)	High	7	CoreValve	All-cause mortality	1 year post-procedure	TAVR is superior over SAVR in high surgical risk
PARTNER II Cohort A (18)	82	2032 (1011/1021)	Intermediate	6	SAPIEN XT	Non-hierarchical composite of death and disabling stroke	2 years post-procedure	TAVR is non-inferior to SAVR in intermediate surgical risk
SURTAVI (19)	80	1660 (864/796)	Intermediate	4.5	CoreValve, Evolut R	All-cause mortality or disabling stroke	2 years post-procedure	TAVR is non-inferior to SAVR in intermediate surgical risk

*Comparator was optimal medical therapy
TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality;

Table 2. Overview of complication rates in landmark TAVR trials, 30 days post-procedure

Trial	Risk category	30 day mortality		Paravalvular AR (≥moderate)		Permanent PM		Stroke or TIA		Major vascular complication	
		TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
PARTNER 1 Cohort B (10)	Extreme	5.0%	2.8%*	12%	NA*	3.4%	5.0%*	6.7%	1.7%*	16.2%	1.1%*
PARTNER 1 Cohort A (11)	High	3.4%	6.5%	12.2%	0.9%	3.8%	3.6%	5.5%	2.4%	11%	3.2%
Medtronic CoreValve ® U.S. Pivotal Trial (13)	High	3.3%	4.5%	9.0%	1.0%	19.8%	7.1%	5.7%	6.5%	5.9%	1.7%
PARTNER II Cohort A (18)	Intermediate	3.9%	4.1%	3.7%	0.6%	8.5%	6.9%	6.4%	6.5%	7.9%	5.0%
SURTAVI (19)	Intermediate	2.0%	1.3%	3.4%**	0.3%**	25.9%	6.6%	3.4%	5.3%	6.0%	1.1%

*comparator was optimal medical therapy

**at discharge

AR, aortic regurgitation; PM, pacemaker; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack;

Table 3. Overview of complication rates in landmark TAVR trials, at the longest available follow-up

Trial	Risk category	Longest available follow-up	Mortality		Paravalvular AR (≥moderate)		Stroke or TIA	
			TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
PARTNER 1 Cohort B (70)	Extreme	5 years	71.8%	93.6%*	NR	NR	16.0%◦	18.2%◦*
PARTNER 1 Cohort A(71)	High	5 years	67.8%	62.4%	NR	NR	15.9%	14.7%
Medtronic CoreValve® U.S. Pivotal Trial (72)	High	3 years	32.9%	39.1%	5.9%	0%	15.2%	21.0%
PARTNER II Cohort A (18)	Intermediate	2 years	16.7%	18.0%	8.0%	0.6%	12.7%	11.0%
SURTAVI (19)	Intermediate	2 years	11.4%	11.6%	4.9%	0%	10.0%	11.0%

*comparator was optimal medical therapy

◦only stroke

AR, aortic regurgitation; NR, not reported; PM, pacemaker; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack;

Table 4. Ongoing Low Risk Trials comparing TAVR and SAVR*

Trial	clinicaltrials.gov identifier	Design	STS-PROM	TAVR device	Estimated total enrollment	Primary endpoint	Time frame for primary endpoint	Estimated completion date for primary endpoint
PARTNER 3	NCT02675114	RCT	<4%	SAPIEN 3	1328	Composite rate of all-cause mortality, all stroke, and re-hospitalization	1 year post-procedure	October 2018
Medtronic Low Risk Trial	NCT02701283	RCT	<3%	CoreValve / EvolutR	1200	All-cause mortality or disabling stroke	2 years post-procedure	March 2018
NOTION 2	NCT02825134	RCT	<4%	Any CE approved TAVR device	992	Composite rate of all-cause mortality, myocardial infarction and stroke	1 year post-procedure	June 2020

TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; RCT, randomized-controlled trial; CE, Conformité Européene; STS-PROM,

*source: www.clinicaltrials.gov