Evolution of Transcatheter Aortic Valve Replacement

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Abstract: Transcatheter aortic valve replacement emerged ≈20 years ago and changed the landscape of structural interventional cardiology. The first experiments in animal models provided proofs of the concept and the substrate for the first percutaneous valve implantation in patients. The initial promising results in a clinical setting drew the attention of the industry and of the scientific community, and an effort was made for the past 12 years to address the limitations of the technology, facilitate the procedure, minimize the risk of complications, and broaden the applications of transcatheter aortic valve replacement. This article reviews the evolution of transcatheter aortic valve replacement, presents the first steps in this field, cites the evidence from registries and clinical trials, highlights the limitations of this treatment, and discusses the future perspectives and the developments proposed to address the current pitfalls. (Circ Res. 2014;114:1037-1051.)

Key Words: aortic valve stenosis ■ prognosis

Severe symptomatic aortic stenosis (AS) is the most frequent valvular heart disease in elderly, and it is associated with poor outcomes if left untreated.1 Surgical aortic valve replacement (SAVR) is the traditional treatment and seems to improve symptoms, quality of life, and prolong survival.2 However, a substantial number of patients (30%–40%) is deemed unsuitable for SAVR because of the multiple comorbidities that they have, which raise considerably the periprocedural risk.3 In 2002, Cribier et al demonstrated for the first time the feasibility of a percutaneous valve implantation in a patient with AS, providing a promising less invasive alternative treatment for valvular heart disease. Since then, an effort was made to address the initial limitations of transcatheter aortic valve replacement (TAVR) technology and broaden its applications. New developments in valves and TAVR enabling devices have reduced the risk of complications, simplified the procedure, and allowed the treatment of more complex anatomies, while evidence from registries and randomized control trials has provided robust data about the efficacy of this therapy which today is regarded as the treatment of choice in inoperable patients and selected high-risk populations.5,6

In this review article, we trace the history of TAVR, describe the first studies in animal models and humans, present the recent technological advances, and discuss the current limitations and future perspectives in the field.

The First Steps

First Attempts for a Less Invasive Treatment of Aortic Valve Disease

In 1965, Davies7 described a catheter-mounted cone-shaped valve that had a parachute configuration which allowed blood to flow toward the peripheral circulation and prevented aortic regurgitation (AR). The device was designed for the treatment of AR, it could be inserted in the ascending aorta through the carotids, and its feasibility was tested in animal models. A few years later, Mouloupoulos et al8 introduced 3 different catheter-mounted valve designs for the treatment of AR. Two prototypes incorporated a balloon that could be positioned percutaneously in the ascending aorta and was inflated at the diastolic phase to prevent AR and deflated at systole to allow free systolic flow. Limitations of these designs were the risk of balloon rupture and the fact that they required an external system that regulated the inflation and deflation of the balloon. The third catheter-mounted valve carried a greater potential for clinical applications because it had an umbrella-shaped design that was able to passively close during systole allowing blood to flow toward the peripheral circulation and open during diastole to prohibit backflow. Phillips et al9 in 1976 introduced a single cusp valve that was mounted onto a catheter which could be advanced in the ascending aorta through the carotid artery. The basic principles of the prototype were similar to the parachute-shaped and umbrella-shaped designs, because the valve was able to close during systole to allow forward flow and open in diastole to block the regurgitant flow. Following the above concept, Matsubara et al10 designed another prototype that consisted of a balloon catheter which incorporated 2 latex check valves that prevented the backward flow during the diastolic phase. Experimental studies provided evidence that the above-mentioned designs were able to reduce AR and the left ventricular (LV) end-diastolic pressure and maintain a normal diastolic pressure. However, none of
them had clinical applications because they could not be implanted and fixed in the aorta or the aortic valve position.

**Balloon Aortic Valvuloplasty**
The first balloon aortic valvuloplasty was performed in 1985 by Cribier et al in an inoperable 77-year-old woman who had severe symptomatic AS. The procedure was uncomplicated and resulted in a >50% decrease in the aortic valve gradient. Although the residual AS remained significant (transvalvular gradient of 40 mm Hg), a striking functional improvement was noted that allowed the patient to resume to normal life. A few weeks later, 2 additional patients underwent successful balloon valvuloplasty by the same research team. These preliminary impressive results attracted attention, and an effort was made to develop special balloons (ie, the Mansfield balloon) that would facilitate the procedure and reduce the risk of complications. However, later reports and the evidence of the Mansfield Aortic Valvuloplasty Registry raised concerns about the safety and efficacy of this approach demonstrating an increased restenosis rate.

**Transcatheter Aortic Valve Implantation**

**First In Vivo Studies**
Andersen et al14 were the first who developed an artificial valve that was suitable for percutaneous implantation. The device consisted of a porcine aortic valve that was mounted onto a stainless steel frame constructed by 2 wires with a diameter of 0.55 mm. Forty to 50 prolene sutures were used to fix the aortic annulus onto the frame. The device was compressed and then mounted onto a deflated 3-foiled balloon dilation catheter (diameter, 41F). Midline laparotomy was performed to reveal the abdominal aorta, and the valve was implanted through the retroperitoneal route in 7 pig models. Apart from 2 prototypes that were deployed in the aortic valve location and obstructed the coronaries, the rest exhibited an excellent hemodynamic performance postimplantation because there was only trivial regurgitation and no significant gradient across the valves. Although the results of this preliminary study were promising, the device did not have clinical applications because the large size of the valve did not allow implantation in humans.

To overcome this limitation, Bonhoeffer et al15 introduced a different design that featured a vein valve which was sutured onto a platinum/iridium stent. After preclinical evaluation in sheep models, the device was successfully used in humans with pulmonary stenosis. However, the proposed design could not be used for the treatment of severe AS because the fragile venous valve could not function in the aortic position where the arterial pressure is high.

**First Human Reports**
The first TAVR procedure was performed on April 16, 2002, by Cribier et al16 and opened new horizons in the treatment of structural valve disease. The treated subject was a 57-year-old inoperable patient with severe symptomatic AS who had balloon aortic valvuloplasty. One week after the valvuloplasty, the patient deteriorated and became hemodynamically unstable because of valve recoil. In view of this life-threatening condition, the percutaneous heart valve was implanted through the retrograde approach. Patient clinical status improved considerably a few hours after TAVR, and the patient was able to resume the off-bed activities. The implanted device exhibited an excellent hemodynamic performance during the first 9 weeks of follow-up. The patient died at the fourth month of follow-up because of noncardiac or procedure-related causes.

Three years later, Panigagua et al17 performed the first TAVR through the retrograde route. The deployed device had a crossing profile of 16F and was implanted through the transfemoral access. Although the valve seemed to function well and there was an initial improvement in patient clinical status, the third postprocedural day the patient suddenly developed respiratory distress and refractory hypotension and was treated for pulmonary embolism but he died 2 days later.

**First Clinical Studies**
The Initial Registry of EndoVascular Implantation of Valves in Europe (I-REVIVE) and the Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) were the first trials that examined the feasibility of TAVR. Most of the patients included in these studies were treated through the antegrade approach. The procedural success rate was only 75%, whereas the complication rate was 22%. The patients who had successful uncomplicated TAVR experienced a considerable amelioration of their symptoms, but had poor prognosis (at 6 months, the major adverse cardiovascular event rate was 37%) that was attributed to the multiple comorbidities that they had.

In 2006, Webb et al18 introduced a modified delivery system that facilitated the deployment of the prosthesis through the retrograde route, and few years later, Walther et al19 introduced...
the transapical approach. These advances facilitated the procedure and enabled its use in a broad number of patients.

**TAVR: Evidence From Registries and Randomized Control Trials**

Cumulative results from registries and large-scale studies have provided robust data about TAVR and demonstrated its efficacy in the treatment of patients with AS (Table). As it is shown in the Table, there was a gradual improvement in the outcomes and a reduction in complication rates which should be attributed not only to the fact that the interventionists have become familiar with the procedure, but also to the technological advances that have increased the safety of TAVR.

The Placement of Aortic Transcatheter Valves (PARTNER) Cohort B study was the first randomized control trial that examined the prognostic implications of TAVR in inoperable patients and demonstrated that patients treated with TAVR had a lower mortality rate compared with those treated only with medications, or with medications and balloon aortic valvuloplasty (20.5% mortality in the TAVR group at 1-year follow-up versus 44.6% in the control group; hazard ratio, 0.39; 95% confidence interval, 0.27-0.56; P<0.001). A year later, the PARTNER Cohort A study was reported. This trial compared the safety and efficacy of TAVR and of SAVR in high operative risk patients. Although there were no differences in mortality at 1- (24.2% for the TAVR group and 26.8% for the SAVR group; P=0.44) and at 2-year follow-up (33.9% for the TAVR arm and 35.0% for the SAVR arm; P=0.78), the patients undergoing TAVR were more likely to sustain a neurological event (11.2% versus 6.5%; P=0.05) or major vascular complications (11.6% versus 3.8%; P<0.001), whereas the patients treated with SAVR demonstrated more major bleedings (29.5% versus 19%; P=0.002) at 2-year follow-up. The STACCATO trial compared the efficacy of transapical TAVR and of SAVR in elderly (aged >75 years) low-risk patients. The study was prematurely terminated after randomizing only 70 patients because there was an excess of adverse events in the TAVR arm (overall event rate: 35.3% in the TAVR group versus 8.3% in the SAVR group). Finally, the recently reported CoreValve US Pivotal extreme risk iliofemoral study that included 471 high-risk patients (with a >50% predicted operative mortality or serious irreversible morbidity at 30 days) implanted with the CoreValve prosthesis (Medtronic Inc, Minneapolis, MN) demonstrated that TAVR is associated with improved outcomes in this inoperable population.

The results of registries and randomized control trials allowed us to not only appreciate the clinical usefulness of TAVR treatment—TAVR has been recently introduced in the updated European guidelines on valvular heart disease as the treatment of choice in inoperable patients and as an effective alternative in selected high-risk populations—but also appreciate the limitations of the technology. During the last years, an effort has been made to identify subjects who would benefit from the procedure, and develop advanced valves and TAVR enabling devices that would reduce the risk complications and broaden the applications of TAVR. The following sections discuss the caveats of TAVR, give an overview of the current and upcoming technological developments, and present the future perspectives in the field.

**Caveats of TAVR**

**Cerebrovascular Events**

Numerous imaging studies have shown an increased incidence of new cerebral ischemic defects in patients undergoing TAVR. These defects seem to have an embolic cause as demonstrated in a recent study Van Mieghem et al demonstrated that during TAVR embolic debris are liberated from the native aortic valve and the aorta and travel to cerebral circulation. Although in most cases the patients with new ischemic defects are asymptomatic, the incidence of stroke after TAVR is relatively high (≤5.2% in some studies) and is regarded as a major pitfall of TAVR. Most of the cerebrovascular events (CVEs) occur within the first days after device implantation, but the risk of stoke remains high for the first 2 months. A severely stenotic and calcified aortic valve, the use of large delivery systems, and multiple manipulations during device implantation (ie, balloon postdilation and device repositioning) have been associated with an increased risk of debris embolization, whereas brain hyperfusion during device implantation has been considered as another possible cause of CVE. Finally, new onset atrial arrhythmias and fibrillation (which is noted in up to one third of the patients undergoing TAVR) may also promote emboli formation and embolization and were found to be predictors of the CVEs that occur between the first 24 hours and the first 2 months postprocedural.

To reduce the incidence of CVEs after TAVR, 3 mechanical cerebral embolic protection devices have been developed, namely, the Claret CE Pro (Claret Medical, Inc. Santa Rosa, CA), the Triguard (Keystone Heart, Caesarea, Israel), and the Embrella embolic deflector (Edwards Lifesciences Inc, Irvine, CA; Figure 1). The first behaves as a debris collector device and has acquired a Conformité Européenne (CE) mark approval, whereas the other 2 act as debris deflectors (the Triguard is also a CE mark approved device). In the DEFLECT I study, the use of the Triguard device was associated with a reduction in the incidence of new ischemic defects in patients undergoing TAVR, whereas in the Prospective Randomized Outcome study in patient undergoing TAVI to Examine Cerebral Ischemia and Bleeding Complications (PROTAVR-C) study, Embrella did not reduce the occurrence of new ischemic defects. The value of the cerebral embolic protection devices in reducing the risk of stroke has not been proven yet.

Antiplatelet therapy is strongly recommended in patients undergoing TAVR, but there is limited evidence about the type and the duration of the regime. In the recently published ACCF/AATS/SCAI/STS guidelines, dual antiplatelet treatment with aspirin and clopidogrel has been proposed, but there is no indication about the duration and the loading dose of clopidogrel. A histopathologic study has demonstrated that 3 months are required for the CoreValve prosthesis to become fully endothelialized indicating that dual antiplatelet treatment should be given for ≥3 months. However, a small randomized control trial that included 90 patients undergoing TAVR showed no difference in prognosis between patients treated with dual antiplatelet treatment and those receiving only aspirin. A larger randomized study, the Aspirin versus aspirin and clopidogrel following Transcatheter Aortic
### Table. Safety and Efficacy of TAVR in Different Registries and Randomized Control Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Device Description</th>
<th>No. of Patients Treated With TAVR</th>
<th>Successful Implantation Rate</th>
<th>30-d Mortality</th>
<th>Incidence of Procedural Complications</th>
</tr>
</thead>
</table>
| I-REVINE and RECAST™   | Percutaneous heart valve         | 35                               | 75%                         | 23.1%          | Stroke: 3.7%  
|                        |                                  |                                  |                             |                | Major vascular complications: 0%   |
|                        |                                  |                                  |                             |                | Pacemaker implantation: 3.7%   |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 55.6% |
|                       |                                  |                                  |                             |                | Stroke: 4%              |
| Webb et al²³           | Cribier Edwards valve            | 50                               | 86%                         | 12%            | Stroke: 1.9%  
|                        |                                  |                                  |                             |                | Major vascular complications: 8% |
|                        |                                  |                                  |                             |                | Pacemaker implantation: 2%   |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 6%   |
| Piazza et al²⁴         | CoreValve                        | 646                              | 97.2%                       | 8.0%           | Vascular complications: 1.9%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 9.3%  |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 13.4% |
| Canadian registry²⁵    | Sapien THV, Sapien XT            | 339                              | 93.3%                       | 10.4%          | Stroke: 2.3%  
|                        |                                  |                                  |                             |                | Major vascular complications: 13.0%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 4.9%  |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 6.0%  |
| SOURCE registry²⁶      | Sapien THV                       | 1038                             | 93.8%                       | 8.5%           | Stroke: 2.5%  
|                        |                                  |                                  |                             |                | Major vascular complications: 12.8%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 7%    |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 1.9%  |
| PARTNER Cohort B⁵      | Sapien THV                       | 179                              | 97.8%                       | 5.0%           | Stroke: 6.7%  
|                        |                                  |                                  |                             |                | Major vascular complications: 16.2%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 3.4%  |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 11.8% |
| French registry²⁷      | Sapien THV and CoreValve         | 244                              | 98.3%                       | 12.7%          | Stroke: 3.6%  
|                        |                                  |                                  |                             |                | Vascular complications: 7.3%  |
|                        |                                  |                                  |                             |                | Pacemaker implantation: 11.8%  
|                        |                                  |                                  |                             |                | Moderate or severe AR: 9.5%  |
| German registry²⁸      | Sapien THV, Sapien XT, CoreValve | 697                              | 98.4%                       | 12.4%          | Stroke: 2.8%  
|                        |                                  |                                  |                             |                | Vascular complications: 19.5%  |
|                        |                                  |                                  |                             |                | Pacemaker implantation: 39.3%  
|                        |                                  |                                  |                             |                | Moderate or severe AR: 17.3%  |
| PARTNER Cohort A⁶      | Sapien THV                       | 348                              | 95.4%                       | 3.4%           | Stroke: 4.7%  
|                        |                                  |                                  |                             |                | Major vascular complications: 11.0%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 3.8%  |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 12.2% |
| UK registry²⁹          | Sapien THV and CoreValve         | 870                              | 97.2%                       | 7.1%           | Stroke: 4.1%  
|                        |                                  |                                  |                             |                | Major vascular complications: 6.3%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 16.3%  |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 13.6% |
| Advance registry³⁰     | CoreValve                        | 1015                             | 97.8%                       | 4.5%           | Stroke: 2.9%  
|                        |                                  |                                  |                             |                | Major vascular complications: 10.7%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 26.3%  |
|                        |                                  |                                  |                             |                | Severe AR: 2.1% |
| French registry³¹      | Sapien THV, Sapien XT, CoreValve | 3195                             | 96.9%                       | 9.7%           | Stroke: 4.1%  
|                        |                                  |                                  |                             |                | Major vascular complications: 4.7%  
|                        |                                  |                                  |                             |                | Pacemaker implantation: 15.6%  |
|                        |                                  |                                  |                             |                | Moderate or severe AR: 16.5%  |

(Continued)
Valve Implantation (ARTE) trial, has recently commenced and is anticipated to provide additional evidence about the optimal regime. The study aims to randomize 200 patients to aspirin versus aspirin and clopidogrel and compare the effectiveness of these therapeutic strategies in reducing CVEs (ClinicalTrials.gov, No. NCT01559298).

**Vascular Complications**

The incidence of major vascular complications varies from 10.7% to 33.3% in different studies and registries and depends on the access site, the clinical profile of the treated patients, and the size of the introducer sheaths.\(^5,6,26,30,56,57\) To reduce the risk of vascular complications, alternative access routes have been proposed (ie, the transapical approach, the transaortic, the subclavian, the transaxillary, the transcarotid, and the retroperitoneal access) which can be considered in patients with an unfavorable iliofemoral anatomy.\(^58–62\) In addition, effort has been made to miniaturize the delivery systems and develop valves with a low crossing profile. Recently, Edwards Lifesciences introduced a self-expandable introducer sheath, namely e-Sheath (initial diameter: 14F–20F) that can temporally expand and facilitate the passage of larger prostheses (Figure 1). Terumo has also developed a flexible, hydrophilic-coated, expandable sheath, the Solopath, that seems to be useful for the management of patients with tortuous iliofemoral anatomy.\(^58–62\) In addition, effort has been made to miniaturize the delivery systems and develop valves with a low crossing profile. Recently, Edwards Lifesciences introduced a self-expandable introducer sheath, namely e-Sheath (initial diameter: 14F–20F) that can temporally expand and facilitate the passage of larger prostheses (Figure 1). Terumo has also developed a flexible, hydrophilic-coated, expandable sheath, the Solopath, that seems to be useful for the management of patients with tortuous iliofemoral anatomy.\(^58–62\) Moreover, Colibri Heart valves (LLC Broomfiled, CO) and Edwards Lifesciences have recently designed prostheses, namely the Colibri heart valve and the Centera valve, respectively, that have a low crossing profile and can be implanted with the use of a 14F delivery system. The devices are currently undergoing first in man studies.

The miniaturization of the valves and of the delivery systems has reduced the need for surgical access site interventions (ie, surgical cut-down and vascular repair) and allowed the development of vascular closure devices that provide controlled and safe sealing of the puncture site. Today, 2 devices are available for the transfemoral route, the Prostar (Abbott Vascular Inc, Santa Clara, CA) and the ProGlide (Abbott Vascular, Redwood City, CA), whereas 3 others, the ProMed (ProMed, Santa Clara, CA), the InSeal (InSeal Medical, Caesarea, Israel), and the VivaSure (VivaSure Medical Ltd, Galway, Ireland), undergo first in man study.\(^65,66\) Moreover, the APICA ASC (APICA Cardiovascular, Galway, Ireland) has acquired CE mark approval for transapical closure, whereas the Permaseal (Micro Intervention Devices, Bethlehem, PA), the CardioClose (Entourage Medical Technologies Inc, Menlo Park, CA), and the CardiApex (CARDIAPEX LTD, Or Akiva, Israel) currently undergo first in man evaluation (Figure 1).\(^57\)

**Conduction Disorders**

The incidence of conduction disorders varies in patients implanted with different prostheses and seems to be associated with an increased need for pacemaker implantation that it is higher to the incidence of pacemaker implantation after SAVR.\(^68–71\) Possible causes are: the design of TAVR prostheses which often protrude into the LV outflow tract, the mechanical injury occurring during the predilation or the positioning of the valve, and the risk of trauma of the conduction system by the catheters and the guidewires used in TAVR.\(^68,72,73\)

Several studies attempted to identify predictors of pacemaker implantation following TAVR and demonstrated that an older age, the use of the Medtronic CoreValve revailing system (ie, the incidence of pacemaker implantation in the CoreValve US Pivotal extreme risk iliofemoral study was 22%, whereas in the PARTNER Cohort B trial, in which the Edwards transcatheter heart valve [Edwards Lifesciences Inc, Irvine, CA] was implanted, it was only 3.4%), the presence of right bundle branch block, a low placement of the prosthesis, a porcelain aorta, and valve oversizing are associated with conduction disorders that required pacemaker implantation.\(^5,33,74–86\) The prognostic implications of this complication is under question as 3 studies showed no association between conduction abnormalities and prognosis and only one demonstrated increased mortality in patients who developed left bundle branch block during TAVR.\(^81–84\)

On the contrary, there is robust evidence that conduction disorders have a negative effect on LV systolic function and on patient’s functional status.\(^85,86\) To address this pitfall, the leaflets of most of the second-generation valves have a low placement that permits a minimal protrusion of the device in the LV outflow tract reducing the risk for conduction interference (Figure 2).
Figure 1. Transcatheter aortic valve replacement (TAVR) enabling devices developed to facilitate the procedure and reduce the risk of complications. Images were obtained with permission from Walther et al.47 Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Prosthesis Dysfunction

Suboptimal valve positioning is a common problem in TAVR. The first generation valves (ie, Sapien transcatheter heart valve, Sapien XT [Edwards Lifesciences Inc, Irvine, CA], and the CoreValve) could not be repositioned or retrieved, and thus in case of an erroneous positioning, the device was dysfunctional and the operator had to deploy a second prosthesis. To address these pitfalls, several new (second generation) TAVR valves have been designed that are retrievable, repositionable, or have features that facilitate optimal device deployment. Some of them have already acquired CE mark approval and are available in clinical arena such as the following: the Direct Flow Medical valve (Direct Flow Medical Inc, Santa Rosa, CA) that is both retrievable and repositionable, and in a recent study, it was shown that its deployment is associated with a low incidence of paravalvular leak and periprocedural mortality; the JenaValve (JenaValve, Munich, Germany) that has feelers and anatomic markers that enable correct positioning and a clipping mechanism for device fixation; the Engager (Medtronic Inc, Minneapolis, MN) that is repositionable and has control arms that provide tactile feedback and secure the valve during deployment; the Lotus valve (Boston Scientific, Natick, MA) that is both repositionable and retrievable and has markers and a motorized delivery system for optimal device implantation; and the Symetis Acurate (Symetis SA, Ecublens, Switzerland) and the Portico (St. Jude Medical, St Paul, MN) valve that are repositionable (Figure 2).87–92

Paravalvular AR is a common finding after TAVR. In most cases, the severity of the regurgitant jet is mild, whereas the prevalence of moderate or severe AR in several studies seems to be around 15%.93 Reports have shown that moderate or severe AR after TAVR is associated with worse outcomes and it is an independent predictor of mortality, whereas in the PARTNER study, it was found that even the presence of mild AR was related with worse prognosis.29,31,94,95

Accurate measurement of aortic annulus and correct sizing of the aortic valve prosthesis are essential and seem to reduce the incidence of paravalvular leak.96 Today, several imaging modalities are available for assessing aortic valve dimensions including 2-dimensional or 3-dimensional transthoracic and transesophageal echocardiography, multislice computed tomography, x-ray aortography, and magnetic resonance imaging.97 Two-dimensional echocardiography has been the traditional method for measuring aortic annulus, but recent reports have casted doubts about the efficacy of this technique showing that it underestimates aortic dimensions compared with multislice computed tomography which also provides useful information for treatment planning because it permits evaluation of aortic valve calcification, assessment of the takeoff of the ascending aorta (a horizontal takeoff may hinder correct and coaxial device deployment), and measurement of the distance between aortic valve annulus and left main stem ostium (ie, a low origin of the left main stem has been associated with an increased risk of left main obstruction).98–100

Figure 2. Advantages of the second-generation valves that are anticipated to reduce the risk of complication and broaden the applications of transcatheter aortic valve replacement (TAVR). CE indicates Conformité Européenne.
Recent advances in image processing enabled the design of new imaging systems and data fusion software that allow comprehensive, real-time visualization of the aortic valve anatomy and can be used in the catheterization laboratory for optimal device positioning. Four systems are today available in clinical setting: the C-THV Paieon (Paieon Inc, New York, NY), the DynaCT (Siemens AG, Erlangen, Germany), the 3mensio valve system (3mensio Medical Imaging, Bilthoven, The Netherlands), and the Phillips heart navigator (Phillips, Amsterdam, The Netherlands). The first 2 systems process angiographic data, whereas the other 2 process multislice computed tomographic data and are able to reconstruct the aortic anatomy and define the best angiographic projections for treatment planning (Figure 3).

Small-scale validation studies have shown that they can optimize device positioning and reduce the incidence of paravalvular regurgitation in patients undergoing TAVR.

**Other Complications**

Obstruction of the ostium of the left main stem or of the right coronary artery is a rare adverse event and can be caused...
either by the valve or by a displaced calcified native leaflet. It is more frequent in women and in patients implanted with a balloon-expandable valve and involves mainly the left main stem. A recent analysis that included 6688 patients showed a low incidence of coronary artery obstruction (0.66%), which however was associated with an increased periprocedural and 30-day mortality. The only anatomic predictors of coronary artery obstruction were a low origin of the left main and a shallow sinus of Valsalva that could not accommodate the displaced leaflets.

Myocardial injury, defined as an increase in cardiac enzymes, is seen in almost all the patients undergoing TAVR. It has been attributed to myocardial ischemia caused by the rapid pacing or by potential coronary embolisms, as well as to the direct myocardial trauma occurred during transapical access or by the deployed device that stretches the basal segments of the LV. Rodés-Cabau et al. demonstrated an inverse relation between raised cardiac enzymes and the improvement in the LV ejection fraction post-TAVR, whereas there is conflicting data about the prognostic implications of myocardial injury with 1 small-scale study showing no association between myocardial injury and mortality and another report that included 119 patients demonstrated that myocardial injury was an independent predictor of 30-day mortality.

Intraventricular septal perforation, LV perforation, and peri-cardial effusion are rare complications that have been attributed to the stiff guidewires used in TAVR procedures. Lately, Roy et al. introduced a dedicated TAVR guidewire that has a preshaped curve at its tip which performs ≏1 revolution. The proposed wire is anticipated to reduce the local forces that the other wires exert to the LV during prosthesis implantation and minimize the risk of perforation. A small feasibility study that included 39 patients provided proofs of the concept demonstrating the safety and efficacy of the guidewire. TAVR seems to reduce LV afterload, increase LV ejection fraction, and promote LV remodeling. These changes have a beneficial effect on mitral valve performance, and several reports have shown a decrease in the severity of the mitral regurgitation following TAVR. However, a single study demonstrated that a deeply embedded prosthesis is likely to interfere with the anterior mitral valve leaflet, induce mitral regurgitation, or even cause mitral stenosis. Mitral valve dysfunction after TAVR can also be attributable to the injury of the mitral valve apparatus by the guidewire used to deliver the device.

Other procedural complications that are seen in TAVR and are related with poor outcomes are as follows: aortic hematoma, dissection, or rupture; and ventricular or aortic embolization of the prosthesis.

Future Perspectives in TAVR

Emerging TAVR Technologies

Apart from the valves that have already been used in clinical setting, several other devices have been recently developed and are currently under clinical evaluation. These include the following: the Trinity valve (Transcatheter Technologies, Regensburg, Germany) that is both repositionable and retrievable, the Sapien III valve (Edwards Lifesciences, Irvine, CA) that has a skirt which covers the frame of the valve and is anticipated to reduce the incidence of paravalvular leak, the CoreValve Evolut (Medtronic Inc, Minneapolis, MN) that can be recaptured and repositioned, and the HLT (Heart Valve Technologies Inc, Maple Grove, MN) valve that was implanted for the first time in humans in 2009 where it was found to be associated with an increased risk of complications; the device was redesigned and currently it undergoes first in man study.

In addition, several other new valves are under preclinical evaluation including the following: the AorTx (Cardiac MD, Mountain View, CA) that is both repositionable and retrievable, the Optimum TAV (Thubrikar Aortic Valve Inc, Rapid City, SD) which has a strong self-expanding Nitinol frame that is effective in both bicuspid and tricuspid valves, the UCL TAV (University College of London, London, United Kingdom) which is the only device with polymeric leaflets that are expected to provide the valve increased durability, and the Vanguard II valve (ValveXchange Inc, Greenwood Village, CO) that incorporates an innovative technology which allows in vivo replacement of its leaflets when these begin to fail (Figure 4). Nanotechnology carries a great potential in valve design because it permits the synthesis of structures and devices with small dimensions and unique properties. In 2006, the University of Texas Health Science Center (San Antonio, TX) presented a nanosynthetic valve namely PercValve. Company’s technology involves processing of pure metals inside a specially designed vacuum chamber. The outcome of this process is the generation of an ultrathin pliable metal called eNitinol that is plasticized, can be elongated, and used for the construction of the PercValve. The developed prosthesis has a monolithic design and is expected to emulate the physiological function of a native valve. The leaflets of the valve consist of a microporous membrane with thickness <10 μm that allow fast endothelialization and are mounted onto a self-expanding frame which is surrounded by an expandable membrane that is anticipated to reduce the risk of paravalvular leak. The device is retrievable and repositionable and has low crossing profile (requires a 10F sheath). Animal studies have shown a rapid endothelialization of the leaflets and an excellent short-term functionality of the device. Further evaluation is however required to test the durability of the valve and its long-term efficacy before being implanted in humans.

In 2005, Sutherland et al. designed the first autologous tissue engineering prosthesis that consisted of bone marrow–derived mesenchymal stem cells. The valve was mounted onto a bioreabsorbable frame and was surgically implanted in the pulmonary valve of animal models. During the last years, attempts were made to develop an autologous tissue engineering aortic valve prosthesis that could be implanted percutaneously. This device is anticipated to grow and remodel following the changes that occur in the human body, adopt the cellular phenotypes and structural organization of the native valve, and have a physiological function and increased durability. The first results in animals are encouraging; however, additional technological advances are needed to improve the
design of the valve, and research is required to confirm the safety and long-term efficacy of the device before having application in the clinical arena.

From the above, it is apparent that a whole industry has been developed around TAVR and considerable effort has been made to create advanced devices that will minimize the risk of complications, facilitate the procedure, and broaden the applications of TAVR. The commercial aspect of these innovations and the trade laws play a significant role in this field and sometimes regulate the technological evolution. There was recently in Germany, which constitutes the leading TAVR market in Europe, a court case with regards to a patent between 2 leading device companies. This commercial conflict between the 2 major players in industry is likely to have implications in research because it will deprive a considerable amount of money that will be spent for litigation fees and affect other small companies that may become more reluctant in investing money for research and development as they could not afford legal battles.

Patient Assessment and Risk Stratification

The assessment of patients referred for TAVR is often a difficult task because these subjects are elderly and have many comorbidities. Therefore, a multidisciplinary approach has been proposed for this purpose which may involve not only the heart team (clinical cardiologists, interventional cardiologists,
cardio-surgeons, and anesthetists), but also additional specialities. This process allows a detailed and accurate evaluation of the candidate patients, but it is also laborious and time consuming.

The clinical risk models that have been developed to predict outcomes following SAVR such as the EuroScore, the EuroScore II, the logistic EuroScore, the Society of Thoracic Surgeons, and the Society of Thoracic Surgeons Predicted Risk of Mortality (PROM) have a low accuracy in predicting mortality after TAVR because they do not take into account factors such as frailty or patient’s specific anatomic characteristics (ie, the presence of an unfolded aorta, a porcelain aorta, the iliofemoral anatomy, etc) that are related with an increased risk of complications and affect prognosis in TAVR. In a recent report, Van Mieghem et al proposed a new risk stratification model specially designed for patients undergoing TAVR, the so-called SURTAVI model. The proposed model includes not only common variables found in previous risk models such as age, diabetes mellitus, renal insufficiency, cerebrovascular disease, but also variables that seem to affect outcomes in patients undergoing TAVR such as frailty, the presence of a porcelain aorta, a complex chest deformity, previous extensive mediastinal radiation, and advanced liver failure. Limitations of the proposed model are the fact that it does not include anatomic features which have been associated with an increased risk of complications, such as a tortuous iliofemoral anatomy and low position of the ostium of the coronaries, and the fact that it has not been validated in clinical setting yet.

Growing Indications

Recent evidence from small-scale studies in low-risk patients has demonstrated that TAVR may have a role in the treatment of intermediate- or low-risk surgical subjects. Two randomized control trials, the PARTNER II Cohort A (ClinicalTrials.gov, No. NCT01314313) and the SURGical and Transcatheter Aortic Valve Implantation (SURTAVI) trial (ClinicalTrials.gov, No. NCT01586910), have been designed to explore this potential and have recently commenced. Both are noninferiority studies that randomize intermediate-risk patients to TAVR and SAVR at 1:1 basis and aim to compare the safety and efficacy of these 2 treatment strategies.

The value of TAVR in severe pure AR has been explored by 2 small-scale studies. In the first, 43 patients were treated with the Medtronic CoreValve prosthesis. There was an increased incidence of significant postprocedural AR (7 patients had at postprocedure AR grade II and 2 had grade III), and 18.6% of the patients required a second valve implantation. These suboptimal results were attributed to the complexity of the aortic valve anatomy, to the dilated aortic root that is often seen in these patients, and to the lack of calcification that can facilitate device fixation. In the second study, a second-generation valve, the JenaValve, was used for the treatment of pure AR. The proposed device has significant advantages compared with the CoreValve because it is repositionable, has positioning feelers that enable correct deployment, and includes a clip—fixation mechanism for optimal device fixation. The device was tested in 5 patients, the procedure was successful in all cases, there was no need for a second device deployment, and no significant regurgitation was detected on echocardiography at postprocedure. Although these small-scale studies have demonstrated the potential of TAVR in pure AR, further research is required to design valves that will be effective in this setting, define the anatomy that is suitable for this treatment, and optimize valve sizing.

Redo cardiac surgery in patients with a failing bioprosthesis is often associated with an increased operative risk especially in elderly patients with many comorbidities. Several studies investigated the role of TAVR in treating high-risk patients with a degenerated bioprosthesis. The reported results confirmed the feasibility of this approach, demonstrating however an increased transvalvular gradient post-TAVR which was attributed to the suboptimal expansion of the valve which was constrained within the small surgical bioprosthesis. Intermediate-term follow-up data are provided in one study which showed that the implanted prostheses function well at 1 year; however, long-term follow-up data are not available today.

Conclusions

During the last years, TAVR has gradually matured, established as an effective treatment, and changed the landscape of interventional cardiology. Cumulative evidence from large-scale studies has demonstrated its efficacy, whereas recent technological advances have overcome the limitations of the first devices, facilitated the procedure, and reduced the risk of complications. The future is expected to be more prosperous since data from ongoing trials will allow us to stratify patients more accurately, while new developments in TAVR technology will permit us to expand its applications and establish TAVR as the first-line treatment in a broad spectrum of patients.

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Disclosures

None.

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