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Transcatheter Aortic Valve Implantation (TAVI): Is it Time for This Intervention to be Applied in a Lower Risk Population?

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ABSTRACT: Patients with severe aortic stenosis are sometimes not candidates for conventional open heart surgery because of severe deconditioning, excessive risk factors, and multiple comorbidities. Transcatheter aortic valve implantation (TAVI) is a relatively recent intervention, which was initially addressed to individuals with severe symptomatic aortic stenosis at substantial or prohibitive surgical risk. Despite the documented beneficial effects of this therapeutic intervention in certain carefully selected individuals, it has not yet been applied to lower risk patients. This is a review of the current literature and accumulated clinical data of this rapidly evolving invasive procedure in an attempt to resolve whether it can now be applied to a wider portion of patients with aortic stenosis.

KEYWORDS: TAVI, severe aortic stenosis

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What is TAVI?

Transcatheter aortic valve implantation is a relatively recent intervention, which was initially addressed to individuals with severe symptomatic aortic stenosis at prohibitive surgical risk. This invasive intervention was initially introduced experimentally and it was first performed in humans in 2002 by Cribier and colleagues.[1] Since then, several large multicenter registries, as well as prospective randomized trials have confirmed with definitive clinical data that this therapeutic modality is a feasible and effective alternative to traditional surgical aortic valve replacement (SAVR) in high-risk and non-operable patients.[2–4]

Epidemiology and Clinical Implications of Severe Aortic Stenosis

Aortic stenosis is the most common acquired valve condition in the western world, and its prevalence is suggested to be increasing proportionally with age. The prevalence of severe symptomatic aortic stenosis is approximately 3% in those aged over 75 years, but this percentage rises steeply with increasing age. Aortic valve stenosis results from the progressive accumulation of fibrous tissue and calcific degeneration on an anatomically normal valve or on a disrupted one because of a previous episode of rheumatic fever. About 1–2% of the population is born with a bicuspid aortic valve.[5] While bicuspid valves may function normally, such individuals are at increased risk of developing severe stenosis because of a degenerative effect, possibly attributed to hydrodynamic stress. It has been suggested that the histopathologic changes that occur on calcific aortic valve leaflets resemble skeletal bone formation.[6]

Severe aortic stenosis results in pressure overload and left ventricular concentric hypertrophy.[7] The progressive valve narrowing and the pathophysiologic adaptive mechanisms

cause symptoms such as shortness of breath, chest pain, and syncope. Severe aortic stenosis, which is accompanied by symptoms, is considered to be a fatal disease if left untreated. The annual mortality in such individuals is estimated to be 25%, and average survival is only 2 to 3 years. Severe aortic valve stenosis primarily affects old individuals, and it constitutes a major health problem in developed countries, as it is the most prevalent cardiovascular condition after hypertension and coronary artery disease.[8]

Traditional Therapeutic Intervention in Aortic Stenosis

Considering its dismal prognosis, symptomatic patients with severe aortic stenosis should be referred promptly for aortic valve replacement (SAVR). SAVR reduces symptoms and improves survival in patients who are not at high risk for perioperative morbidity or mortality.[9] It is emphasized that age is not a contraindication for surgery, but comorbid disease may make surgical risk unacceptable.

Surgical risk can be estimated using online risk calculators from the Society of Thoracic Surgeons (STS; http://www.sts.org) or the European System for Cardiac Operative Risk Evaluation (EuroSCORE; http://www.euroscore.org). The STS score has a trend to underestimate risk for SAVR, whereas the logistic EuroSCORE overestimates risk for isolated valve surgery.[10] Several clinical and technical parameters are not included in those risk scores, such as an extensively calcified (porcelain) aorta, oxygen-dependent respiratory insufficiency, liver cirrhosis, history of chest wall radiation or deformity, immobility, dementia, and frailty; these will need to be included in the calculation when a definitive and reliable SAVR/TAVI risk score is eventually developed. According to the STS database, in-hospital mortality for isolated AVR was found to be 2.6% and stroke rate of 1.3%.[11] According to the same source, several other complications have been associated with traditional SAVR, such as myocardial infarction, bleeding, infection, atrial fibrillation (AF), atrioventricular (AV) heart block, and acute kidney injury (AKI). Advanced age, female sex, impaired left ventricular systolic function, congestive heart failure, and associated coronary artery disease are known to be clinical factors associated with a higher rate of complications.

Surgical options for aortic stenosis include SAVR with a mechanical or bioprosthetic (heterograft) valve, SAVR with an allograft (homograft) valve, and pulmonic valve autotransplantation (Ross operation). Mechanical prosthetic designs include single tilting-disk prostheses and bileaflet prostheses. Bioprosthetic valves can be stented or stentless and are reasonable in patients who want to avoid the risks and inconvenience of anticoagulation. Bioprosthetic valve durability is improving but may not be as good as a mechanical valve. A novel option for surgical valve replacement is the implementation of a rapid deployment valve (EDWARDS INTUITY rapid deployment valve, Edwards Lifesciences, Irvine, CA, USA). Rapid deployment and sutureless valves are associated with significantly reduced myocardial ischemic and cardiopulmonary bypass times and are associated with excellent hemodynamic performance and acceptable rates of pacemaker implantation and paravalvular leak. Such devices have gained increasing clinical acceptance particularly in Europe with almost 3000 total implants to date.[12] Prosthetic valve complications include structural deterioration, symptomatic valve prosthesis–patient mismatch, thrombosis, embolism, bleeding complications from anticoagulation, endocarditis, tissue ingrowth, and hemolysis from periprosthetic aortic regurgitation.

The Untreated Population – Conservative Management

The natural history of untreated severe aortic stenosis is well established. It is suggested that an average decrement of 0.1 cm^2 per year occurs in aortic valve once the diagnosis is made.[13] Development of symptoms such as angina, syncope, and dyspnea on effort is associated with an unfavorable prognosis and warrants prompt intervention with aortic valve replacement. Without intervention, the mortality is estimated to be as high as 75% in 3 years after symptoms develop.[14]

Several drugs have been used in an attempt to conservatively regress progression of valve stenosis, such as statins, angiotensin-converting enzyme inhibitors, and bisphosphonates. However, no definitive benefit was demonstrated with pharmaceutical interventions.[15] On the other hand, surgical intervention and aortic valve replacement normalize life expectancy of symptomatic patients with aortic stenosis to that of matched controls.[16] Several advantages of open heart surgery, such as direct visualization of the valve while on cardiopulmonary bypass and also many years of accumulated clinical experience, have rightfully established it as the gold standard of treatment for such patients. Furthermore, advancements in surgical technique, prosthetic valve design, and anesthesia seem to steadily improve the outcomes over the years.

Unfortunately, many patients with severe aortic stenosis are not candidates for conventional open heart surgery because of severe deconditioning, excessive risk factors, and multiple comorbidities. The suggested therapeutic interventions for such patients are aortic valvuloplasty and transcatheter aortic valve intervention. In large randomized trials and registries, the transcatheter procedure has been documented to significantly improve long-term survival compared with medical management alone in inoperable patients and to have a similar benefit to that of surgery in the high-risk population.

An Overview of the Technical Aspects of TAVI

TAVI requires to be performed in a hybrid operative suite especially designed to be able to accommodate the necessary equipment and adequately trained personnel. In order to achieve optimal results, the procedure requires a multidisciplinary team, including a cardiac surgeon, an interventional cardiologist, and a cardiac anesthesiologist experienced in

transesophageal echocardiography. Other team members include a surgical assistant, a surgical scrub nurse trained in such demanding procedures, a circulating nurse, and a radiology or catheterization laboratory technician.

The procedure is usually performed under general anesthesia and occasionally under mild sedation and local anesthesia. The desired activated clotting time (ACT) is achieved with heparin administered intravenously. Throughout the procedure, echocardiography and fluoroscopy are implemented in order to continuously assess the anatomical requirements for TAVI and guide the procedure.

The retrograde approach, which is most commonly performed, involves insertion of the delivery catheter through the common femoral artery. In the antegrade approach, a small left anterior mini-thoracotomy is performed to expose the apex of the heart; the left ventricular apex is then punctured in order to introduce the guidewires and sheaths, perform balloon valvuloplasty, and insert the delivery sheath that carries the valve.

Currently, the most commonly used prostheses in clinical practice are the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, California, USA) and the CoreValve System (Medtronic Inc., Minneapolis, Minnesota, USA). In order to address the issue of optimal positioning of transcatheter aortic valve prostheses, three new devices have been launched lately: the Medtronic Engager™ System, the Symetis Accurate™ Valve, and the JenaValve™. These valves are designed for transapical implantation and have different mechanisms to facilitate positioning in an anatomically oriented position.

The Edwards SAPIEN transcatheter aortic valve is a bioprosthetic valve made of bovine pericardial tissue mounted into a balloon-expandable stainless steel frame. The SAPIEN-XT valve is currently manufactured with diameters of 20, 23, 26, and 29 mm. Next-generation SAPIEN valve systems are currently undergoing evaluation, and will incorporate additional leaflet, frame, and sealing enhancements to improve deliverability, positioning, and sealing. The 23-mm and 26-mm Edwards SAPIEN transcatheter aortic valves are most commonly applied and are suitable for a native aortic annulus measuring 18 to 25 mm. The third-generation Edwards SAPIEN XT THV cobalt–chromium bovine pericardial valve has a lower crimp profile and a modified leaflet design. The SAPIEN valve is placed using a retrograde (transarterial – usually femoral) or antegrade (transapical) approach. The latter technique is especially addressed to individuals with a compromised peripheral vascular system.

The CoreValve transcatheter aortic valve is a trileaflet bioprosthetic porcine pericardium prosthesis mounted into a self-expanding nitinol frame. The CoreValve 26-mm and 29-mm prostheses are suitable for an aortic annulus measuring 20 to 27 mm. It is also available in a diameter of 31 mm. Before implantation of the SAPIEN valve, the native aortic valve is pre-dilated with a balloon. A temporary transvenous pacing wire positioned in the right ventricle enables rapid ventricular pacing during balloon valvuloplasty. This maneuver is an essential step during valve deployment in order to prevent malpositioning and embolization of the prosthesis.[17] An aortic root angiography is mandatory in order to confirm the intra-annular position of the valve relative to the coronary ostia.

Several newer transcatheter valves are in various stages of evaluation, such as the Lotus™ valve (Boston Scientific Inc., MN, USA), the Direct Flow™ valve (Direct Flow Medical Inc., CA, USA), the CENTERA valve (Edwards Lifesciences Inc., CA, USA), and SAPIEN 3™ valve (Edwards Lifesciences, Irvine, California, USA). Some of these have already been applied in clinical practice; however, experience and data remain limited. The new prosthetic devices are designed in order to facilitate better deliverability, adequate positioning, and reduced leakage. It is also expected that these new and improved prosthetic devices will significantly reduce vascular complications, since they will be compatible with 14 to 16 French expandable sheath delivery systems.

Feasibility and Risks of TAVI

Perioperative complications are occasionally encountered in TAVI, such as malpositioning or migration/distal embolization of the valve, the need to convert urgently into open surgery, renal failure, advanced degree AV block that needs to be managed with pacemaker implantation, stroke, and myocardial infarction.[18]

Although it is infrequently encountered, prosthesis dislocation during TAVI is a dreadful complication. It can be managed by implanting a second device and leaving the dislocated valve safely in the descending aorta or, if possible, by complete retrieval of the migrated device.[19] A retrieval of valve is associated with a high risk for vascular complications and embolic stroke.

Vascular complications. Transfemoral TAVI (TF-TAVI) is associated with a higher rate of vascular complications in comparison to the transapical TAVI (TA-TAVI).[20] The technical improvement and the implementation of a sheath of reduced size lead to a significant reduction in vascular complications.[21] Appropriate selection of patients is possible after a thorough preoperative evaluation of the peripheral vascular system with the use of advanced imaging techniques (vascular CT scan and angiography). This strategy may reduce vascular complications. The use of a percutaneous arterial closure device has been suggested to be associated with an increased rate of vascular complications.[20] However, this remains to be clarified with clinical experience and upcoming randomized trials. Established risk factors for TAVI-associated major bleedings are female gender, use of a large size delivery system, compromised peripheral vascular system, percutaneous access, and the need for urgent valve retrieval.[22]

The most common vascular complications after TAVI are arterial bleeding and arterial occlusion, which are usually treated surgically. However, a percutaneous approach may also be used and is associated with an acceptable clinical outcome.[23]

Bleeding after TAVI is directly proportional to the incidence of vascular complications. It is now established that patients who require blood transfusion following TAVI exhibit an increased risk of major stroke and kidney dysfunction, as well as increased mortality at 1 year.[24] Reduced bleeding complications and less need for blood transfusion may improve outcomes in TAVI.

Stroke. Stroke remains one of the most fearful complications in TAVI patients. Cerebrovascular events are more frequent in TAVI compared to SAVR, and their incidence is associated with reduced survival.[25] Most of the strokes occur during the procedure or shortly after. Post-procedural brain injury is partially attributed to a substantial amount of cerebral microemboli.[26] The phenomenon of TAVI-associated cerebral microembolism was evaluated with magnetic resonance imaging (MRI), which demonstrated new foci of reduced diffusion. Most of the cases of microembolism seem to occur during manipulation of the aortic root and valve by guide wires and catheters and during implantation of the prosthesis. Older age, lower body mass index, prior stroke, and AF are documented as risk factors of stroke in TAVI patients.[22] According to the same study, which included 389 patients, the incidence of stroke was 3.6%. In a different series of 214 patients who underwent TAVI with the use of CoreValve, an increased incidence of stroke was reported (9%) in the perioperative period.[27] The need for post-dilatation of the prosthetic valve and new-onset AF increase the risk of stroke in the acute period. Late cerebrovascular events have also been recorded (3.3%) at a median follow-up of 12 months. Chronic AF and prior cerebrovascular disease are considered to be predictors of such late events. The selected access route substantially influences the incidence of stroke; the lowest stroke rate was observed with the TA approach (2.7%).

After TAVI, many patients exhibit a higher rate of cognitive decline in comparison with SAVR. Imaging studies following TAVI showed new embolic events in 72.0%; however, only 6.6% of those patients presented with clinically significant neurological deficits.[26] The clinical relevance of this form of silent cerebral ischemia remains to be resolved.

The incidence of embolic events associated with TAVI is suggested to be reduced with the use of a protection device that is inserted through the radial or femoral artery and is placed on the aortic arch. The implantation of cerebral protection devices is associated with a significant cost. It also requires a certain level of expertise. Although the clinical data regarding its use are promising, it is currently suggested to be used in selected individuals with a history of documented cerebrovascular disease and significant calcification of the aortic valve.[28]

Renal failure. AKI is a documented complication after TAVI. Its incidence ranges from 12% to 21%. Although in the majority of the cases AKI is reversible, it may worsen the 1-year survival.[29] Diabetes mellitus, peripheral vascular disease, renal failure, and the need for blood transfusions increase the incidence of AKI. It is suggested that TA-TAVI increases the likelihood of kidney injury.[30] However, this assumption could be possibly biased by the fact that most of the patients who undergo TA-TAVI suffer from advanced peripheral vascular disease.

Paravalvular leak. Adequate sealing between the prosthesis and the annulus is often not possible because of the irregular and heavily calcified borders of the native valve. Consequently, the risk of paravalvular leak following TAVI is increased. Mild insufficiency of the prosthetic valve is found in about 70% of patients after TAVI.[31] Severe calcific degeneration of the annulus and the presence of a bicuspid aortic valve are significant risk factors for paravalvular leak after TAVI. Preoperative cardiac computed tomography allows an accurate assessment of the degree of valve calcification and also a precise measurement of the elliptically shaped annulus in order to minimize the risk of prosthesis mismatch.[32] Moderate or severe paravalvular leakage after TAVI is found in 15% to 20%. The severity of a paravalvular insufficiency after TAVI is very important; it is established to correlate with 1-year mortality.[33,34] If severe paravalvular leak is identified, then careful post-dilatation may be attempted for better expansion of the prosthetic device. Prosthesis oversizing is suggested by some investigators as a way to achieve adequate adaptation to the aortic annulus, and thus minimize the leakage.[35] However, this approach has not yet been extensively investigated.

AV block. Permanent pacemaker implantation because of AV block is required in 10–50% of patients following TAVI.[36] The conduction disturbance, which is caused by iatrogenic damage to the bundle of His or the AV node, usually develops within 3–7 days, so close electrocardiographic monitoring is mandatory in this period.[37] The incidence of complete AV block and the requirement of permanent pacemaker are estimated to be 6% with the use of Sapien valve (either transapical or transfemoral) and 26% with the use of CoreValve.[38] The presence of right bundle branch block (RBBB) and the implantation of a large valve are both independently correlated with a higher risk of post-TAVI complete AV block.[39]

What is the Evidence so far for TAVI? (Registries and Trials)

Registries. Several large European and Canadian registries have been published, showing excellent results after TAVI using both the TF and TA approach.[40] One of the largest registries reported to date is the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry.[38] Overall, 1038 patients were enrolled at 32 European centers and were treated with either a TF or a TA approach. Patients treated by TA approach had more comorbidities at baseline compared to TF patients, resulting in a substantially higher EuroSCORE (29.1 vs 25.7%; $P = 0.001$). Procedural success was 95.2% and 92.7% and 30-day mortality was 6.3% and 10.3% in the TF and TA populations, respectively. In early 2011, 1-year results

were published, demonstrating a 1-year survival of 76.1% overall, 72.1% for TA and 81.1% for TF patients. A number of large dedicated CoreValve registries have been reported; generally, these have been somewhat larger than Edwards registries. In fact, the most promising 3-year results were reported by Ussia et al.[41] This registry included 1015 patients from 44 experienced centers between March 2010 and July 2011. The mean logistic EuroSCORE was 19.2%. At 30 days and 6 months, the rate of all-cause mortality was 4.5% and 12.8%, respectively, with cardiac mortality of 3.4% and 8.4%, respectively. This registry provides insights into contemporary TAVI data of experienced operators and is regarded as a benchmark for comparing outcomes.

One of the largest registries to date was reported by the FRANCE 2 (FRench Aortic National CoreValve and Edwards) investigators.[42] This registry included 3195 patients treated between January 2010 and December 2011 at 34 centers. The registry reflects contemporary real-life use of available TAVI devices in patients at a high surgical risk; the Edwards SAPIEN and the Medtronic CoreValve devices were used in 66.9% and 33.1%, respectively. The TF approach was most popular (74.6%), followed by TA (17.8%) and subclavian (5.8%), while 1.8% underwent some other approach. The procedural success rate was 96.9% and 1-year survival in patients was 76.0%.

The largest series of patients who underwent TAVI or SAVR is reported in the German Aortic Valve Registry (GARY).[43] A total of 13,860 consecutive patients undergoing repair for aortic valve disease, either conventional surgery or catheter-based techniques, have been enrolled in this registry. It is noted that in this particular registry, patients undergoing catheter-based techniques were significantly older and had a higher risk profile. The stroke rate was low in all groups with 1.3% (AVR), 1.9% (AVR + CABG), 1.7% (TF-TAVI), and 2.3% (TA-TAVI). The in-hospital mortality was 2.1% (SAVR) and 4.5% (SAVR + CABG) for patients undergoing conventional surgery and 5.1% (TF-TAVI) and 7.7% (TA-TAVI) for patients undergoing catheter-based techniques.

Trials. While registry reports are of crucial value to assess the use of TAVI in the real world, more rigorous assessments are available from the multi-centered randomized clinical Placement of Aortic Transcatheter Valve (PARTNER) trials.[44,45] As the first of two parallel trials was completed, the results of PARTNER IB showed that TF-TAVI was superior to standard therapy in patients not deemed candidates for surgery. The primary endpoint of all-cause mortality was markedly reduced by 46% (P = 0.001). Recently reported 2-year outcomes showed continued encouraging results. At 2 years, the primary endpoint of all-cause mortality was reduced from 67.6% in the standard treatment arm to 43.3% in the TAVI arm (P = 0.001). The PARTNER cohort IA compared TAVI with SAVR and met its non-inferiority endpoint: the all-cause 1-year mortality in the TAVI group was non-inferior to the SAVR group (24.2 vs 26.8%; P = 0.44). Some concerns were raised with regard to neurologic events that were higher with TAVI than SAVR at 30 days (5.5 vs 2.4%; P = 0.04) and 1 year (8.3 vs 4.3%; P = 0.04). Although the recently published 2-year results showed that stroke rates were similar for TAVI and SAVR during 1 and 2 years with a hazard ratio of 1.22 (95% CI 0.67–2.23, P = 0.52), the issue of stroke warrants further investigation and should not be underestimated.[46] The rate of the composite of all-cause death and stroke was encouragingly nearly identical after TAVI (37.1%) and SAVR (36.4%) at 2 years (P = 0.85).

What is Recommended by the Guidelines?

According to the European guidelines on valve disease published in 2012, TAVI is recommended for patients with severe symptomatic aortic stenosis, who have been evaluated by the "heart team" as unsuited for conventional surgical treatment because of severe comorbidities.[47] It is important that TAVI is implemented only in hospitals with cardiac surgery on-site. In these guidelines it is also emphasized that eligible patients should have a life expectancy of more than 1 year in order to substantiate a beneficial effect in the quality of life.

In the guidelines published in 2012 by the American College of Cardiology Foundation (ACCF), the establishment of clearly defined patient-selection criteria was attempted.[48] Some criteria can be precisely identified with objective measurements, but many require subjective estimates based on clinical judgment. These subjective assessments are at least as important as the objective determinations and necessarily create some variability in the process of patient selection. As technology improves and experience is gained, it is likely that many of these criteria will change to expand TAVI to different populations that will be optimally treated with the next generation of devices.

Is TAVI Cost-Effective?

PARTNER remains the only randomized controlled trial to compare TAVI with SAVR for patients with severe aortic stenosis. The survival and cost benefits of TAVI compared to medical therapy in inoperable patients have been previously demonstrated.[49] However, optimal treatment for "high-risk" patients remains controversial, and there is conflicting evidence on the cost-effectiveness of TAVI compared to SAVR in different healthcare settings. Reynolds et al performed an economic evaluation of TAVI versus SAVR based on a modified intention-to-treat cohort of 647 patients from the PARTNER A trial, which represents the first cost analysis to separately assess the TF and TA approaches.[50] Results of this study reported that the entire TAVI cohort did not demonstrate significant differences in cost-effectiveness compared with SAVR. However, when stratified according to access site, patients who underwent the TF approach were more likely to be economically attractive compared with SAVR than the TA approach. Compared with the TF group, the TA group had increased comorbidities, which translated into higher periop-

erative mortality and morbidity and therefore reduced cost-effectiveness.

It should be noted that the cost-effectiveness of TAVI compared with SAVR is largely dependent on the cost and duration of postoperative hospitalization. It has been shown that patients who undergo surgery have a longer length of hospitalization compared with TAVI, and this increase in cost largely offsets the more expensive cost of the TAVI valve device. This is clearly demonstrated in the PARTNER trial, where patients who underwent SAVR had mean hospitalization duration of 16 days. The cost analysis performed in this study is based on the American healthcare system, where the cost of hospitalization is much higher, and may be less applicable to other countries. However, substantial evidence in favor of the cost-effectiveness of TAVI is reported in other studies as well.[51,52] Nation-specific economic assessments should be performed in the future, and a systematic review of the cost-effectiveness of TAVI may be warranted.

Is TAVI Better than Conventional AVR?

Currently, the only well-established long-term effective therapeutic management for individuals with severe symptomatic aortic stenosis is surgical valve replacement. However, many patients with severe symptomatic aortic stenosis remain untreated, primarily because of the operative and perioperative risks associated with surgery. This group of 30% to 60% of patients with untreated aortic stenosis has a high mortality rate and needs to be served by the medical community. The available results indicate that TAVI is an acceptable alternative to surgery in selected high-risk patients. Future randomized studies are expected to clarify whether lower-risk patients could benefit from this operation.

Vascular-access complications associated with TAVI are gradually declining, mostly because of the improvement in several technological aspects of the procedure. Stroke remains to be a major and fearful complication of TAVI; common causes include balloon valvuloplasty, the passage of stiff catheters through a sclerotic and heavily calcified aortic arch, the positioning and implantation of the valve itself, and post-dilation. In more recent studies, the incidence of stroke is lower than previously reported, probably because of the use of more flexible and smaller delivery systems.[18,53] The CoreValve can be implanted without prior valvuloplasty, and that alone might reduce the rate of embolization. Embolization-protection devices and deflectors that can redirect emboli from the arch downstream are being developed and evaluated, but no data support the clinical benefit of these devices.

The clinical durability of the valves used for TAVI still remains unknown. In preclinical fatigue tests, the transcatheter valves have shown the same excellent performance as standard biological valves; this applies both to the leaflets and to the stents. The structural failure rate of the current generation of transcatheter valves in clinical trials is very low. Long-term follow-up data are of course lacking.

Finally, another controversial issue is the use of TAVI in a younger, lower-risk population. In many centers, TAVI has become a routine procedure, and the results of recent trials show improved outcomes and safety of the approach.[54] However, the incidence of associated complications, such as paravalvular leak and stroke, and the unknown durability factor are lingering concerns. On the basis of the current data, trials in younger and lower-risk patients are justified. For now, the 2012 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for Heart Valve Disease clearly restrict the indication for TAVI only to a high-risk population, as do the U.S. Food and Drug Administration-approved guidelines.

As the interest of the scientific community regarding TAVI continues to grow and clinical experience is evolving, the results will inevitably become better and the rate of complications will decrease. The accumulated clinical data are expected to lead to better risk stratification for TAVI procedures and manage to identify the patient population that will eventually benefit from this procedure.

Has Anyone used TAVI in Low-Risk Patients?

A study was performed in order to assess clinical outcomes among patients with estimated low or intermediate surgical risk undergoing TAVI.[44] The study included 389 consecutive patients, who underwent TAVI between August 2007 and October 2011. According to this study, low-risk patients undergoing TF-TAVI exhibited the most favorable outcome with no recorded events in terms of all-cause mortality, cerebrovascular accidents, myocardial infarction, major access site complications, and acute renal failure 30 days after the intervention. No differences were observed with regard to cerebrovascular accidents and myocardial infarction during 1-year follow-up. According to this study, TAVI should not be limited to inoperable or STS-defined high-risk patients and should be guided by the decision of an interdisciplinary heart team. Compared with patients at calculated high risk, carefully selected patients with STS-defined intermediate or low risk appear to have favorable clinical outcomes.

Comparison Between AVR and TAVI

High-risk inoperable patients. According to the European SOURCE registry, the 1-year survival of very high risk patients (logistic EuroSCORE of ≥40%) was 59.2% and 72.5% after TA-TAVI and TF-TAVI, respectively.[38] The PARTNER study cohort B was a randomized trial, which recruited inoperable individuals with severe symptomatic aortic stenosis and an STS score of 11.6 ± 6.0%.[45] It should be noted that the unsuitability for conventional AVR in a significant portion of patients was attributed to factors that were not accounted by the STS score, such as the presence of porcelain aorta, previous thoracic irradiation, chest wall deformity, oxygen-dependent respiratory insufficiency, and frailty. All-cause mortality at 1 year was 30.7% with TAVI versus 50.7% with

standard therapy. Similar findings have been demonstrated in another study.[44]

High-risk patients. The data, so far, demonstrate that TAVI provides at least comparable benefits in high-risk patients compared to SAVR. High-risk patients are generally defined as those with an STS score of >10% or EuroSCORE of >20%. According to a propensity-matched comparison between conventional aortic valve replacement and TA-TAVI in 92 high-risk patients, there was no statistically significant difference in perioperative death, strokes, infections, re-operation for bleeding, or length of post-operative hospital stay.[45] In PARTNER cohort A, which recruited high-risk SAVR-eligible patients, 1-year all-cause mortality was not statistically significant, 24.2% in the TAVI group and 26.8% in the AVR group, respectively ($P = 0.44$). Only major vascular complications at 30 days were shown to be more prominent in TAVI patients (11.0%) compared to 3.2% in conventional AVR patients ($P < 0.001$).[44]

Moderate-risk patients (STS 5–10%). No studies have yet been performed for direct comparison between TAVI and SAVR in moderate-risk patients. However, perioperative mortality and morbidity in this particular patient population seems to be higher with TAVI than with conventional SAVR. According to the data of one center, patients at moderate risk that underwent TAVI recorded a 30-day mortality of 2.4%, stroke of 2.4%, major adverse cerebrovascular and cardiac events (MACCE) of 5.9%, and pacemaker implantation in 21.4%.[55]

Low-risk patients (STS <5%). According to the 2006 STS database, the reported perioperative mortality and morbidity with conventional isolated SAVR in low-risk patients was extremely low; <1.0% for patients younger than 60 years and 1.3% for those of 60–70 years.[9] Considering those figures and the confirmed durability of surgical results, it is unlikely that TAVI would ever provide better outcomes than AVR in this particular patient population. Currently, conventional SAVR is the standard treatment for aortic stenosis in low-risk patients.

Patient Selection for TAVI

A multidisciplinary team, including cardiologists, cardiovascular surgeons, imaging specialists, and anesthetists, is essential for achieving appropriate patient selection and creating a dedicated and safe procedural environment for TAVI. Patient selection is of paramount importance in order to achieve optimal results. The following criteria are suggested to be used in determining if a patient is suitable for TAVI.

Confirmed severe AS. The echocardiographic criteria to define severe AS include aortic valve area of <1.0 cm^2, indexed aortic valve area of <0.6 cm^2/m^2, and mean transvalvular pressure gradient of >40 mmHg. Patients with severe AS and low cardiac output frequently present with a relatively low transvalvular pressure gradient. In selected patients with the phenomenon of low-flow low-gradient severe AS, stress echocardiography, either with exercise or dobutamine infusion, may be useful to determine the actual severity of valve stenosis. If stress results in increases in stroke volume and aortic valve area >0.2 cm^2 with little change in pressure gradient, it is likely that the baseline severity of AS is overestimated. In contrast, patients with true severe AS likely have a fixed valve area with increases in stroke volume and pressure gradient during a stress state.

Defining high-risk or inoperable patients. TAVI should be currently reserved for patients who meet standard indications for SAVR but are defined as high-risk for operative mortality with conventional AVR. Several predictive risk models derived from large surgical databases have been developed in an attempt to identify those patients who will derive more benefits from a nonconventional therapeutic approach. The two most common models are the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the STS Risk Calculator. It is agreed that a logistic EuroSCORE greater than 20% or an STS score higher than 10% is associated with high-risk for conventional AVR. Nevertheless, these risk models are not accurate and consistent, particularly in the elderly population; the logistic EuroSCORE overestimates operative risk, while the STS score may underestimate it. Apart from that many risk factors are not well reflected by the scoring systems, especially end-stage liver disease, prolonged preoperative hospital stay, general deconditioning, frailty, immobility because of other medical conditions, obesity, severity of peripheral vascular and aortic disease, previous chest wall radiation, porcelain aorta, and degree of lung disease.

Assessing benefits of TAVI. It is a reasonable requirement that candidates for TAVI should have a meaningful quality of life with a minimum life expectancy of greater than 1 year. For patients with end-stage diseases, such as end-stage liver disease and Chronic Obstructive Pulmonary Disease (COPD), severe dementia, limited functional capacity, extreme frailty, and end-stage malignancy, TAVI may offer no benefit.

Anatomical and technical suitability for TAVI. After appropriate patient selection, a thorough assessment for anatomical and technical suitability should be performed. The implementation of several diagnostic imaging modalities such as coronary angiography, transthoracic/transesophageal echocardiography, and CT imaging is mandatory before proceeding to TAVI. CT provides multiple measurements of the aortic annulus size, and it is regarded to be more accurate compared to transesophageal echo for determination of the appropriate transcatheter valve size. Several anatomical factors should be investigated in detail, such as the load of calcific degeneration of the valve, the size of aortic annulus and left ventricular outflow tract, the morphology of aortic root, sinotubular junction dimension and calcification, the systolic function of the left ventricle, the origin and anatomy of coronary arteries, because of the potential risk for ostial

obstruction, the presence of intracavitary thrombus, and vascular access.

Currently, the relative or absolute contraindications for balloon-expandable Edwards Sapien™ valve are a bicuspid aortic valve with minimal calcification, aortic annulus size of ≥29 mm, large mobile atheroma in the ascending aorta and aortic arch, the presence of left ventricular or atrial thrombus, concomitant significant mitral valve disease with significant mitral annular calcification, a substantially high anatomical risk for coronary ostial obstruction, severe impairment of left ventricular function, and infective endocarditis. Regarding the use of the CoreValve, an aortic annular size <20 mm or >27 mm is currently regarded to be a contraindication.

What is Expected in the Future?

New generations of the Edwards SAPIEN and the CoreValve are being developed. The 29-mm version of the Edwards SAPIEN inserted through the transapical route and the 23-mm and 31-mm CoreValve devices are now available. Furthermore, devices are being developed in order to allow reposition and retrieval of the prosthesis, and also techniques are designed and implemented in order to minimize as possible the degree of paravalvular insufficiency. These devices are in the preliminary stages of evaluation, and as yet, none of them are CE marked. The advent of new technologies may mean improved procedural success rates with better long-term outcomes, but as yet, it is too early to ascertain the exact details of the next generation of widely available transcatheter valve devices.

The size of the delivery system has been reduced in recent years from previously 24 French to the actual 18–19 or even less. Furthermore, the CoreValve delivery sheath has been recently introduced as a smaller, 16-F version. This is expected to significantly reduce TAVI-related vascular complications. Even smaller introducers have been announced by manufacturers and are anticipated to be available in the near future. Specific scores are needed to identify the patients who are at higher risk for TAVI-related vascular complications; this knowledge would enable providers to select a different access route in these patients when appropriate.

With the improvement in the proficiency of TAVI centers and individual operators, this procedure is expected to be applied in a wider array of patients. The accumulated experience in the management of patients with several comorbid factors and anatomic and functional variables currently allows the implementation of TAVI in some off-label indications.

Valve-in-valve TAVI. TAVI may now be performed with good results for the management of bioprosthetic aortic valve failure, which results either in stenosis or insufficiency. Currently this remains an off-label indication for TAVI, but it is actually an effective and feasible option for this particularly high-risk group of patients.[56]

Bicuspid aortic valve. Because of the predominantly elliptical shape of bicuspid aortic valve, adequate and complete expansion of a percutaneous valve was initially accepted with skepticism. However, careful case selection now permits the implementation of TAVI in such patients with very good results.[57]

Medium- and low-risk surgical groups. The percutaneous valve implantation in patients with a low surgical risk remains a controversial issue.[58] The growing confidence and accumulated experience of the operators is believed to eventually expand the use of TAVI to a wider portion of the population.[59] However, a longer follow-up is definitely required before TAVI is safely labeled as a viable alternative to conventional surgical treatment in low-risk individuals.

"No access patients". The currently accepted access routes for TAVI are transfemoral, transapical, and transaxillary/subclavian. A new TAVI approach through the transaortic route has been recently used in a few patients in whom the above options are not available.[60] This appears to be a feasible technique for the delivery of the CoreValve prosthesis with promising short-term results.

Aortic regurgitation. The use of TAVI for isolated severe symptomatic aortic regurgitation has been reported in a small number of patients and is expected to grow as experience builds up.[61] Aortic insufficiency remains at the moment an off-label use of TAVI.

Conclusion

Current clinical data clearly show that TAVI is a feasible alternative to conventional surgical replacement of aortic valve in carefully selected individuals with severe comorbidities. It is very important to know the potential complications in order to recognize them early and treat them accordingly. Further clinical investigation is expected to identify which patients respond favorably to each specific valve and access route. By individualizing the technical aspects of the procedure of TAVI to each patient's anatomy and general condition, the outcome will eventually improve. Therefore, only after the accumulation of sufficient clinical data the indication for TAVI may be expanded to intermediate- and lower-risk patients with aortic stenosis.

In younger (particularly <65 years) high-risk patients with high logistic EuroSCORE (>20%) or STS score (>10), SAVR may be preferred given the unknown durability of TAVI and a higher incidence of paravalvular leakage. Risk assessment with the establishment of reliable, reproducible, and realistic scores is eagerly awaited to be improved. Patients with porcelain aorta, previous operation with patent coronary bypass grafts, physical deformities restricting sternal access, and frailty are special subgroups for whom TAVI may offer advantages, regardless of the STS risk score. It is believed that a combination of objective quantitative predictive risk models, objective measurement of frailty, and subjective assessments by experienced surgeons is the ideal/best way to characterize individual risks.

Author Contributions

Conceived the concepts: IP. Analyzed the data: IP. Wrote the first draft of the manuscript: IP. Contributed to the writing

of the manuscript: IP. Agree with manuscript results and conclusions: IP, EN. Jointly developed the structure and arguments for the paper: IP. Made critical revisions and approved final version: IP, EN. Both authors reviewed and approved of the final manuscript.

REFERENCES

1. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis. First human case description. *Circulation*. 2002;106:3006–8.
2. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic bioprosthesis European outcome (SOURCE) registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2010;122:62–9.
3. Eltchaninoff H, Prat A, Gilard M, et al. FRANCE Registry Investigators. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. *Eur Heart J*. 2011;32:191–7.
4. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high risk patients with severe aortic stenosis. The UK TAVI (United Kingdom Transcatheter Aortic Valve Implantation) registry. *J Am Coll Cardiol*. 2011;58:2130–8.
5. Michelena HI, Desjardins VA, Avierinos JF, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation*. 2008;117(21):2776–84.
6. Mohler ER, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. *Circulation*. 2001;103(11):1522–8.
7. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol*. 1997;29(3):630–4.
8. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol*. 2011;8(3):162–72.
9. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation*. 2010;121:151–6.
10. Osswald BR, Gegouskov V, Badowski-Zyla D, et al. Overestimation of aortic valve replacement risk by EuroSCORE: implications for percutaneous valve replacement. *Eur Heart J*. 2009;30:74–80.
11. Webb J, Cribier A. Percutaneous transarterial aortic valve implantation: what do we know? *Eur Heart J*. 2011;32:140–7.
12. Borger MA, Dohmen P, Misfeld M, Mohr FW. Current trends in aortic valve replacement: development of the rapid deployment EDWARDS INTUITY valve system. *Expert Rev Med Devices*. 2013;10:461–70.
13. Otto CM, Pearlman AS, Gardner CL. Hemodynamic progression of aortic stenosis in adults assessed by Doppler echocardiography. *J Am Coll Cardiol*. 1989;13:545–50.
14. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. *Ann Thorac Surg*. 2006;82:2111–5.
15. Cowell SJ, Newby DE, Prescott RJ, et al. Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med*. 2005;352:2389–97.
16. Ussia GP, Barbanti M, Sarkar K, et al. Transcatheter aortic bioprosthesis dislocation: technical aspects and midterm follow-up. *EuroIntervention*. 2012;11:1285–92.
17. Khawaja MZ, Sohal M, Valli H, et al. Standalone balloon aortic valvuloplasty: indications and outcomes from the UK in the transcatheter valve era. *Catheter Cardiovasc Interv*. 2013;81:366–73.
18. Stratiev V, Guyon P, Teiger E, Collet JP. Reducing the risk of vascular complications during percutaneous aortic valve replacement. *Ann Cardiol Angéiol*. 2012;61:281–6.
19. Van Mieghem NM, Tchetche D, Chieffo A, et al. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. *Am J Cardiol*. 2012;110:1361–7.
20. Stortecky S, Wenaweser P, Diehm N, et al. Percutaneous management of vascular complications in patients undergoing transcatheter aortic valve implantation. *Cardiovasc Interv*. 2012;5:515–24.
21. Tchetche D, Van der Boon RM, Dumonteil N. Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: insights from the Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative. *Am Heart J*. 2012;164:402–9.
22. Stortecky S, Windecker S, Pilgrim T, et al. Cerebrovascular accidents complicating transcatheter aortic valve implantation: frequency, timing and impact on outcomes. *EuroIntervention*. 2012;12:62–70.
23. Reinsfelt B, Westerlind A, Ioanes D, et al. Transcranial Doppler microembolic signals and serum marker evidence of brain injury during transcatheter aortic valve implantation. *Acta Anaesthesiol Scand*. 2012;56:240–7.
24. Pilgrim T. Predictors of clinical outcomes in patients with severe aortic stenosis undergoing TAVI: a multistate analysis. *Circulation*. 2012;5:856–61.
25. Nuis RJ, Van Mieghem NM, Schultz CJ, et al. Frequency and causes of stroke during or after transcatheter aortic valve implantation. *Am J Cardiol*. 2012;109:1637–43.
26. Nombela-Franco L, Webb JG, de Jaegere PP, et al. Timing, predictive factors and prognostic value of cerebrovascular events in a large cohort of patients undergoing transcatheter aortic valve implantation. *Circulation*. 2012;126:3041–53.
27. Ghanem A, Müller A, Sinning JM, et al. Prognostic value of cerebral injury following transfemoral aortic valve implantation. *Eurointervention*. 2012;8:1296–306.
28. Onsea K, Agostoni P, Samim M, et al. First-in-man experience with a new embolic deflection device in transcatheter aortic valve interventions. *EuroIntervention*. 2012;8:51–6.
29. Kong WY, Yong G, Irish A. Incidence, risk factors and prognosis of acute kidney injury after transcatheter aortic valve implantation. *Nephrology*. 2012;17:445–51.
30. Saia F, Ciuca C, Taglieri N, et al. Acute kidney injury following transcatheter aortic valve implantation: incidence, predictors and clinical outcome. *Int J Cardiol*. 2013;68(2):1034–40.
31. Tarantini G, Gasparetto V, Napodano M, Fraccaro C, Gerosa G, Isabella G. Valvular leak after transcatheter aortic valve implantation: a clinician update on epidemiology, pathophysiology and clinical implications. *Am J Cardiovasc Dis*. 2011;1:312–20.
32. Takagi K, Latib A, Al-Lamee R, et al. Predictors of moderate-to-severe paravalvular aortic regurgitation immediately after CoreValve implantation and the impact of postdilatation. *Catheter Cardiovasc Interv*. 2011;78:432–43.
33. Abdel-Wahab M, Zahn R, Horack M, et al. German Transcatheter Aortic Valve Interventions Registry Investigators. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry. *Heart*. 2011;97(11):899–906.
34. Sherif MA, Abdel-Wahab M, Stöcker B, et al. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. *J Am Coll Cardiol*. 2010;56:1623–9.
35. Piazza N, Grube E, Gerckens U, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention*. 2008;4:242–9.
36. Schroeter T, Linke A, Haensig M, et al. Predictors of permanent pacemaker implantation after Medtronic CoreValve bioprosthesis implantation. *Europace*. 2012;14:1759–63.
37. Bleiziffer S, Ruge H, Hörer J, et al. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *Cardiovasc Interv*. 2010;5:524–30.
38. Thomas M, Schymik G, Walther T, et al. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2011;124:425–33.
39. Erkapic D, Kim WK, Weber M, et al. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. *Europace*. 2010;12:1188–90.
40. Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol*. 2010;55:1080–90.
41. Ussia GP, Barbanti M, Petronio AS, et al. on behalf of CoreValve Italian Registry Investigators. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. *Eur Heart J*. 2012;33:969–76.
42. Gilard M, Eltchaninoff H, Iung B, et al. FRANC 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med*. 2012;366:1705–15.
43. Hamm CW, Möllmann H, Holzhey D, et al. The German Aortic Valve Registry (GARY): in-hospital outcome. *Eur Heart J*. 2014;35:1588–98.
44. Leon MB, Smith CR, Mack M, et al. PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–607.
45. Smith CR, Leon MB, Mack MJ, et al. PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–98.
46. Kodali SK, Williams MR, Smith CR, et al. PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686–95.
47. Vahanian A, Alfieri O, Andreotti F, et al. The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451–96.

48. Holmes DR Jr, Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2012;59(13):1200–54.
49. Reynolds MR, Magnuson EA, Wang K. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis. *Circulation*. 2012;125:1102–9.
50. Reynolds M, Magnuson E, Lei Y. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis. *J Am Coll Cardiol*. 2012;60:2683–92.
51. Neyt M, Van Brabandt H, Devriese S, Van De Sande S. A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population. *BMJ Open*. 2012;2:e001032.
52. Osnabrugge R, Head S, Genders T. Costs of transcatheter versus surgical arotic valve replacement in intermediate risk patients. *Ann Thorac Surg*. 2012;94: 1954–60.
53. Kodali SK, O'Neill WW, Moses JW, et al. Early and late (one year) outcomes following transcatheter aortic valve implantation in patients with severe aortic stenosis (from the United States REVIVAL trial). *Am J Cardiol*. 2011;107:1058–64.
54. Wenaweser P, Stortecky S, Schwander S, et al. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. *Eur Heart J*. 2013;34(25):1894–905.
55. Higgins J, Ye J, Humphries KH, et al. Early clinical outcomes after transapical aortic valve implantation: a propensity-matched comparison with conventional aortic valve replacement. *J Thorac Cardiovasc Surg*. 2011;142:47–52.
56. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. *Circulation*. 2010;121:1848–57.
57. Chiam PT, Chao VT, Tan SY, et al. Percutaneous transcatheter heart valve implantation in a bicuspid aortic valve. *JACC Cardiovasc Interv*. 2010; 3:559–61.
58. Kojodjojo P, Gohil N, Barker D, et al. Outcomes of elderly patients aged 80 and over with symptomatic, severe aortic stenosis: impact of patient's choice of refusing aortic valve replacement on survival. *QJM*. 2008;101:567–73.
59. Brown JM, O'Brien SM, Wu C, Sikora JA, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *J Thorac Cardiovasc Surg*. 2009;137:82–90.
60. Latsios G, Gerckens U, Grube E. Transaortic transcatheter aortic valve implantation: a novel approach for the truly "no-access option" patients. *Catheter Cardiovasc Interv*. 2010;75:1129–36.
61. Ducrocq G, Himbert D, Hvass U, Vahanian A. Compassionate aortic valve implantation for severe aortic regurgitation. *J Thorac Cardiovasc Surg*. 2010;140:930–2.