REVIEW ARTICLE

New advances in the prevention of transcatheter aortic valve implantation failure: current and future perspectives

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) represents an established and safe therapeutic alternative to surgical valve replacement for patients with severe symptomatic aortic stenosis. However, some uncertainty still persists about long-term outcomes of this procedure. The aim of this review was to analyze the actual state of the art with focus on the new advances that are being developed to improve this therapeutic approach. Thanks to improvements in technology and materials as well as a substantial standardization of the procedure, patients undergoing TAVI are showing increasing life expectancy. Although a growing body of evidence demonstrated a convincing midterm safety profile, the very long-term survival after TAVI still depends on the rate of bioprosthetic valve failure (BVF). Structural valve deterioration, leaflet thrombosis, prosthesis–patient mismatch, paravalvular regurgitation, and endocarditis are the main complications that threaten the preservation of valvular function. Through the understanding of these physiopathological mechanisms underlying BVF, we analyzed how the management of such valve-related issues has evolved in the last years and how current clinical and research efforts are shifting towards the ambit of prevention of valve failure. In conclusion, in the near future, the prevention of long-term BVF is expected to be one of the major challenges regarding TAVI. Currently, promising results can be observed in the development of new technologies and therapeutic options.

Introduction Severe aortic valve stenosis is a disease with growing incidence affecting millions of people worldwide due to the ageing of the population.[1] In the last years, transcatheter aortic valve implantation (TAVI) has progressively become the answer to this issue, offering a valid alternative for patients with symptomatic severe aortic disease at high-risk for complications or death from surgery. Nowadays, thanks to the recent favorable data[2] and the technical improvements,[3] TAVI indication has been extended to medium and low-risk patients.[4,5] Therefore, understanding outcome predictors[6,7] and long-term valve implantation criticalities have become of pivotal importance. Although bioprosthetic valves present a lower risk of thrombosis as compared with mechanical ones, they are more likely prone to structural valve degeneration (SVD), resulting in limited durability. The long-term suitability of TAVI is still a matter of debate and studies or registries reporting outcomes beyond 5-year follow-up[8-10] are scarce, hampering the assessment of real incidence of transcatheter valve failure.[11] All the above formed the basis for our review, in which we sought to evaluate the risk factors, mechanisms, and current and future advances capable of preventing TAVI failure.

Definition of structural valve deterioration and bioprosthetic valve failure "Valve degeneration" and "valve failure" are different concepts worth to be defined. Structural valve degeneration is one of the most likely causes of bioprosthetic breakdown, but the etiopathogenesis of valve failure is not always valve dependent.

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Prosthesis malposition and mismatch, intra- or paravalvular regurgitation (PVR), endocarditis, and thrombosis could represent the main causes of the hemodynamic deterioration of the valve even without a direct involvement of valvular structures. Moreover, SVD often represents a subclinical process, thus, its impact is insufficient to explain the severity of the valvular failure by itself.

Several studies[12,13] tried to standardize the main features and clinical findings to correctly define what SVD actually means. Historically, in the surgical field, reoperation rate instead of valve performance characteristics was used to define valve durability, and it is reasonable to assume that the real SVD incidence was underestimated. Nowadays, with the newer generation of bioprosthetic pericardial valves, incidence of SVD is estimated to be 2% to 10% at 10 years.[14] However, some studies reported that about 25% to 35% of patients treated with a bioprosthetic valve present some degree of valve degeneration at the Doppler echocardiographic exam within 10 years.[15]

More recently, to better define long-term durability in the field of TAVI, a new definition of bioprosthetic valve failure (BVF) was advanced by the consensus of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Society of Cardiology (ESC), and the European Association for Cardio-Thoracic Surgery (EACTS)[16] which proposed BVF as the new outcome of interest in studies assessing the long-term performance of TAVI. According to the consensus, the definition of BVF is as follows: 1) autopsy findings of bioprosthetic valve dysfunction likely related to the cause of death, or "valve-related death," defined as any death caused by valve dysfunction in the absence of confirmatory autopsy; 2) aortic valve reintervention (ie, valve-in-valve TAVI, paravalvular leak closure, or surgical valve replacement); and 3) severe hemodynamic SVD (defined as mean transprosthetic gradient ≥40 mm Hg or an increase of ≥20 mm Hg from baseline; new severe intraprosthetic aortic regurgitation or worsening [>2+/4+] from baseline).

Mechanisms and risk factors of transcatheter aortic valve implantation failure According to the current literature, the main causes of TAVI failure may be categorized into 4 categories: SVD, nonstructural valve deterioration (NSVD), thrombosis, and endocarditis (TABLE 1 and FIGURE 1).

Structural valve deterioration Structural valve deterioration includes all the intrinsic permanent changes in the valve structure causing deterioration and hemodynamic dysfunction. The pathophysiology leading to SVD is complex and not completely understood. It involves mechanical, hematologic, and immunologic causes.

The continuous mechanical stress and the consequent local inflammation may lead to leaflet fibrosis, tears, and perforations. Bioprosthetic valves are made of nonvital tissue, thus any mechanical or immunologic damage persists and may worsen over time, without the opportunity to regenerate or recover. Moreover, the immunohistochemical environment generated around

TABLE 1 TAVI failure mechanisms

Type	Incidence, %	Mechanisms	Effects
Structural valve deterioration	2–10[a]	• Mechanical stress • Local inflammation • Immuno-mediated calcification • Cardiovascular risk factors	• Leaflets malcoaptation • Restenosis • Increased transvalvular gradients
Nonstructural valve deterioration	18–36	• Incorrect valve position • Paravalvular regurgitation • Prosthesis-patient mismatch	• TAVI-in-TAVI • Increased mortality • Increased LVEDP
Leaflets thrombosis	4.8	• Blood stagnation • Large valve diameters • SAPT • Valve-in-valve	• Increased transvalvular gradients • Subclinical and clinical ischemic events
Endocarditis	0.2–3.4	• Valve-in-valve • Malposition • Vascular access site complications and infections • Cardiovascular risk factors	• Increased transvalvular gradients • Embolic events • Sepsis

a At 10 years

Abbreviations: LVEDP, left ventricular end-diastolic pressure; SAPT, single antiplatelet therapy; TAVI, transcatheter aortic valve implantation

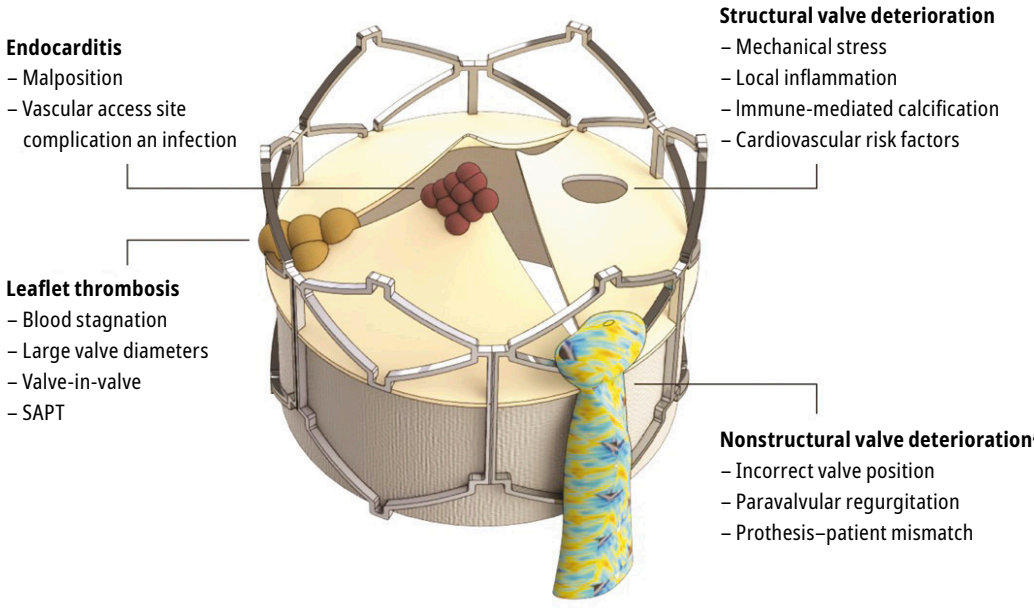

FIGURE 1 Bioprosthetic valve failure mechanisms
a Echocardiographic aliasing
Abbreviations: see TABLE 1

the bioprosthetic valve, promoting calcium crystal nucleation[17] and low-grade immune rejection, leads to leaflet remodeling and thickening. This continuous manipulation of the valve over time generates coaptation deficit and/or restenosis phenomena, causing progressive hemodynamic impairments and increasing prosthetic gradients. Furthermore, several studies suggest that patients' risk factors for atherosclerosis accelerate the degeneration of aortic pericardial valves, affecting their long-term durability.[18] Metabolic syndrome, smoking, high BMI, hypertension, dyslipidemia, renal insufficiency, abnormal calcium-phosphorus metabolism (eg, hyperparathyroidism) may all be involved in the valve life expectancy[19,20] favoring mechanical stress of the leaflets and inflammatory local lesions. A systematic follow-up and the secondary prevention of cardiovascular risk factors may play an important role overall.

Nonstructural valve deterioration The incorrect valve positioning, intravalvular regurgitation or PVR, and prosthesis-patient mismatch (PPM) are the main causes of NSVD.

Malposition (a too high or too low implantation) has been described as the primary cause of early valve failure mainly leading to significant PVR. In some cases, PVR can be reduced to a milder degree with post-dilation but in a small percentage of cases (1.7%–3.9%), interventional cardiologists are forced to perform a valve-in-valve TAVI as a bailout strategy which is often associated with poorer outcomes.[21] Moreover, secondary valve migration or embolization are rare but fearsome sequelae of malposition. The most important predictors of these adverse events are the use of self-expanding or first-generation prostheses and the presence of a bicuspid aortic valve.[22]

More frequent and more severe PVR has been reported after TAVI than after surgical aortic valve replacement (SAVR) with a rate of incidence ranging from 1% to 3% for moderate PVR to 29% to 36% for mild PVR.[23] In the PARTNER (Placement of Aortic Transcatheter Valve) trial,[24] at 1-year follow-up, the worsening of PVR was found to be associated with a significant increase in mortality and hospitalizations. After multivariate adjustments, the presence of moderate-to-severe PVR was related with higher late mortality rate. More disturbingly, 2-year results from the PARTNER trial showed that even mild PVR was associated with significant mortality.[25] These results were subsequently confirmed in observational studies.[26,27]

PPM occurs after TAVI when the effective orifice area of the prosthesis is too small in relation to the patient's body surface area and its incidence may vary from 18% or 20% to 35%.[28] The unsuitable dimension of the valve determines less favorable changes in transvalvular hemodynamics[29] with a persistently elevated postprocedural left ventricular filling pressure and higher trans-aortic valve gradient. Although the clinical impact of severe PPM remains largely unknown, recently it has been associated with increased mid-term mortality and rehospitalizations for heart failure.[30]

The adoption of preemptive strategies through correct procedure planning and early identification and management of periprocedural complications are definitely the key factors to avoid NSVD and long-term BVF.

Thrombosis Leaflet thrombosis (LT), especially when clinically detected, is infrequent after TAVI. Despite a similar incidence of LT in TAVI as compared to SAVR, the time of presentation of such phenomenon seems to differ, appearing to be significantly later after SAVR than following TAVI (3.72 years vs 9.6 months).[31] Recent studies using computed tomography (CT) confirmed subclinical LT in a significant number of patients who had undergone TAVI[32-34] but the clinical long-term implications are uncertain. Indeed, it is still unclear whether subclinical LT might progress to a clinical state and whether subclinical manifestations might have any impact on long-term outcomes. However, it is plausible that the occurrence of subclinical valve thrombosis may be a trigger for a local inflammatory processes and fibrocalcific remodeling. In this regard, a long-term prophylactic antithrombotic strategy preventing LT appears to be of paramount importance, even though there is no strong evidence in the literature on the real efficacy in patients with subclinical LT.

Endocarditis Infective endocarditis, given a less invasive procedural approach, is an unusual complication after TAVI, with a reported annual incidence between 0.2% to 3.4% in retrospective analyses and international registries.[35] Aortic regurgitation severity, high transvalvular pressure gradient, valve-in-valve procedure, low TAVI implantation interfering with mitral valve closure and vascular access site complications were reported as procedure-related risk factors.[36] Prevention of periprocedural infection complications are of importance since an in-hospital mortality rate of 40% was reported in their presence.[36]

Prevention of bioprosthetic valve failure: new advances

Since the first TAVI procedure performed in 2002,[37] progressive and continuous improvements in valve technology and materials have been achieved. Increased operators' experience and skills, newer generation valve designs, and standardization of the procedures were the key factors that minimized periprocedural complications and reduced long-term adverse events.[38,39] Nowadays, new frontiers of research need to face various issues related to longer life expectancy of patients with valves and therefore should focus the attention on prevention of long-term bioprosthetic valve dysfunction (TABLE 2).

New materials and valve design Technical developments have matured over the last 10 years in terms of valve materials and designs. Newer valves progressively reduced complications and improved periprocedural outcomes.[40] The new low-profile systems are conceived to better fit the native valve anatomy and to decrease the risk of thrombosis. The latest generation of bioprosthetic valves such as the Sapien 3 Ultra, CoreValve Evolute Pro, Lotus Edge are the last of a long series of attempts to improve valve performance. The introduction of taller antileak skirt associated with a facilitated valve deployment is expected to further reduce the incidence of PVR and procedural time of intervention. In this regard, the Lotus valve system (Boston Scientific, Massachusetts, United States), thanks to a complex delivery system designed to facilitate repositioning and retrieval, is able to accomplish the correct placement of the valve before the final release, even in the fully expanded position. Moreover, the prosthesis, designed not to block the blood flow through the aortic outflow tract during implantation, can be better hemodynamically tolerated because it does not need the rapid ventricular pacing to establish a functional standstill of the heart. Recently, Grygier et al[41] demonstrated the feasibility of this procedure in high-risk patients, with excellent periprocedural outcomes.

TABLE 2 Studies on antithrombotic regimen after transcatheter aortic valve implantation (patients with no OAC indication)

Study	Design	FU, mo	Sample	Medical regimen	Findings
ARTE[59]	RCT	3	222	Aspirin monotherapy vs aspirin + clopidogrel	MACE not different (7.2%) vs (15.3%); $P = 0.07$ Less bleeding events in SAPT at 3 months (3.6%) vs (10.8%); $P = 0.04$
D'Ascenzo et al[51]	Observational study (propensity score-matched)	45	1210	Aspirin monotherapy vs aspirin + clopidogrel	Higher death (4.5% vs 1.5%; $P < 0.001$) and major bleedings risk (4% vs 1.6%; $P < 0.001$) in the DAPT group
Sherwood et al[60]	Observational study	12	16 694	Aspirin or clopidogrel vs aspirin + clopidogrel	Higher bleeding risk in DAPT (adjusted HR [95% CI], 1.48 [1.1–1.99])
GALILEO[57]	RCT	17	1653	Rivaroxaban + aspirin vs aspirin + clopidogrel	Higher risk of death in rivaroxaban group (HR [95% CI], 1.69 [1.13–2.53]) and higher risk of bleeding (HR [95% CI], 1.5 [0.95–2.37])

Abbreviations: DAPT, dual antiplatelet therapy; FU, follow-up; HR, hazard ratio; MACE, major adverse cardiovascular event; OAC, oral anticoagulant; RCT, randomized controlled trial; others, see TABLE 1

The immunity challenge As studies suggested, antibody-mediated inflammation promotes bio-valves calcification and innovative anticalcification leaflet technologies are finally facing the issue of reducing the immune injury of the valves.[42] Chemical fixation of the leaflets, already a cornerstone of last-generation valves, eliminates the immunogenicity of protein antigens but not the immunogenic stimulus of carbohydrate antigens. The principal antigen involved is galactose-α1,3-galactose (gal) and high quantity of anti-gal antibody have been found in humans.[43] New frontiers of genetic engineering are exploring the way to eliminate gal antigens from the xenogeneic tissue. Gal-free animal tissues from gal-transferase knockout pigs, unable to produce and express gal in their cells, may lead to the development of bioprosthetic valve unaffected by anti-gal antibody–mediated injury,[44] revolutionizing the field of xenotransplantation.

Paravalvular leak closure devices There is the paucity of data regarding the best strategy for paravalvular leak complications after TAVI and their management remains largely dependent on institutions and operators without a shared consensus by scientific societies. Postdilatation and valve-in-valve TAVI are considered the most commonly used strategies, but in the last years, concerns about safety and efficacy have been raised.[45,46]

Recently, some innovative percutaneous closure devices, like the Amplatzer vascular plug, have been released on the market. These devices may have the potential to treat severe hemodynamic impairment with less invasive approaches and without a forceful expansion of the valve. Although it appears to be an attractive additional treatment option, with the described overall success rate of 82.1%,[47] this procedure is often underutilized. The technical difficulty, the struggle to identify the culprit area, the off-label use of vascular plugs not conceived for PVR closure are the main reasons for its scarce employment. The standardization of the PVR leak closure using ad hoc devices may prevent or at least reduce the need for more invasive actions aimed at avoiding long-term BVF.

Application of 3-dimensional printing An interesting tool that may change our vision of planning cardiovascular interventions is 3-dimensional (3D) printing.[48] New 3D printing technologies right now are frequently used in experimental setting and for educational purposes. The creation of deformable blended-material models may be helpful in the planning of complex procedures, hopefully resulting in an increased rate of successful valve implantations. The development of functional patient-specific models may allow for the improvement of intracardiac devices. In this scenario, custom-made devices could be designed and tested, opening new horizons for personalized patient care.[49]

Medical therapy The optimal medical strategy to protect patients from BVF remains unclear and several studies tried to investigate the optimal trade-off between safety and efficacy.[50,51] Current ESC Guidelines[52] suggest dual antiplatelet therapy (DAPT) regimen for 3 to 6 months until the endothelization of the valve scaffold and then to continue with long-term single antiplatelet therapy. Nevertheless, some authors suggest that oral anticoagulant (OAC) alone may have the same potential benefit of preventing thromboembolic events as antiplatelet therapy, but guaranteeing a major protection from long-term LT. The absence of anticoagulant therapy indeed has been proven to be an independent risk factor for SVD.[53-55] Regarding patients with mandatory indication for OAC (eg, atrial fibrillation), most recent evidence[56] showed that antiplatelet therapy on top of OAC increased the incidence of bleeding without any additional benefit in term of further reduction of thrombotic events, suggesting at least in this population the superiority of OAC monotherapy. While OAC could be considered the optimal medical strategy when chronic oral anticoagulation is mandatory, the same conclusions cannot be extended to patients without a real need for anticoagulation therapy. A recent randomized controlled trial (the GALILEO trial),[57] that compared rivaroxaban plus aspirin versus DAPT in TAVR patients without an OAC indication, showed an increased rate of all-cause mortality in rivaroxaban plus aspirin arm and was therefore prematurely terminated for safety reasons. When unnecessary, OAC on top of antiplatelet therapy apparently showed a worse risk-benefit profile than antiplatelet therapy alone. Despite the controversial results of the GALILEO trial, the potential protective role of OAC monotherapy in the management of patients undergoing TAVI without other indications for anticoagulation is unknown and still under investigation. In particular, the ATLANTIS trial, an ongoing multicenter randomized controlled trial, is testing the eventual superiority of apixaban versus the recommended standard of care strategy in reducing the risk of post-TAVR thromboembolic events. The results of the ATLANTIS trial, along with other pivotal ongoing studies aiming to provide additional insight on this issue (AUREA, ClinicalTrials.gov identifier, NCT01642134; ADAPT TAVR, ClinicalTrials.gov identifier, NCT03284827), will help to assess the best antithrombotic regimen between single antiplatelet therapy, DAPT, and OAC (TABLES 2 and 3).

Future perspective on imaging Recently a new fully automatic method using real-time fusion of 3D transesophageal echocardiography

TABLE 3 Studies on antithrombotic regimen after transcatheter aortic valve implantation (patients with OAC indication)

Study	Design	FU, mo	Sample	Medical regimen	Findings
Altisent et al[61]	Observational study	13	621	VKA monotherapy vs VKA + SAPT / DAPT	No difference in MACE in VKA vs VKA + SAPT / DAPT (13.9%) (16.3%) Higher bleeding risk in VKA + SAPT / DAPT (adjusted HR [95% CI], 1.85 [1.05–3.28]; *P* = 0.04)
Geis et al[62]	Observational study	6	326	DOAC monotherapy vs VKA monotherapy	MACE not significantly different (11% vs 8.1%; *P* = 0.45, respectively)
Vora et al[63]	Observational study	12	1138	OAC vs no OAC	Higher combined endpoint of death, stroke, MI (adjusted HR [95% CI], 1.41 [1.25–1.59]; *P* <0.01) and rehospitalization for major bleeding in the no OAC group (adjusted HR [95% CI], 1.24 [1.1–1.4]; *P* <0.01)
Jochheim et al[64]	Observational study	12	962	DOAC monotherapy vs VKA monotherapy	Higher combined endpoint in the DOAC group (adjusted HR [95% CI], 1.44 [1–2.07]; *P* = 0.05) No differences in bleedings
Kosmidou et al[65]	Observational study	24	933	APT and / or OAC vs no therapy	OAC with APT and APT alone both associated with reduced rates of stroke compared with no OAC or APT (HR [95% CI], 0.43 [0.22–0.85]; *P* = 0.02)
Popular TAVI[56]	RCT	12	313	VKA + clopidogrel vs VKA monotherapy	Higher bleeding risk in the VKA + clopidogrel group (RR, 0.63; 95% CI, 0.43–0.9; *P* = 0.01)

Abbreviations: APT, antiplatelet therapy; DOAC, direct oral anticoagulant; MI, myocardial infarction; RR, relative risk; VKA, vitamin K antagonist; others, see TABLES 1 and 2

and 3D multislice CT images with X-ray on live fluoroscopy was proposed to help physicians during TAVI.[58] This new strategy has the advantage to show more detailed on live images of the implantation site without the contrast medium. The better intraprocedural resolution facilitates the correct deployment of the valve improving its apposition to the aortic annulus. In addition, high resolution CT imaging may become a useful tool in the diagnosis and follow-up of subclinical LT. As previously mentioned, CT demonstrated the ability to reveal subclinical LT in a significant number of patients, but due to the unknown clinical impact of these findings, its routine use is currently not recommended outside of research studies. Nevertheless, after the evidence of an increased transvalvular gradient or a recent episode of stroke / TIA, it could be worthy to consider high-resolution CT to exclude LT.

Conclusions BVF is a multifactorial adverse process involving valve related complications and nonvalve dependent factors, occurring in the early phase after TAVI or developing progressively during the following years. Thanks to the advancing of technologies and the upgrading of valve materials and design, long-term survival after TAVI showed constant improvements with convincing results even in low-risk patients, once considered eligible only for a traditional valve replacement surgery. An optimal preprocedural planning, the appropriate follow-up, the understanding and the early diagnosis of SVD seem to be the key factors to assure long-term patient survival. New advances and technologies face the challenge of preventing overtime deterioration of the physiological bioprosthetic valve propensity, and promising results can be already observed.

ARTICLE INFORMATION

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