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Summary

Until recently, transcatheter aortic valve implantation was restricted to high-risk and inoperable patients. The updated 2017 European Society of Cardiology Guidelines have widened the indication to include intermediate-risk patients, based on two recently published trials (PARTNER 2 and SURTAVI). Moreover, two other recent trials (PARTNER 3 and EVOLUT LOW RISK) have demonstrated similar results with transcatheter aortic valve implantation in low-risk patients. Thus, extension of transcatheter aortic valve implantation to younger patients, who are currently treated by surgical aortic valve replacement, raises the crucial question of bioprosthesis durability. In this translational review, we propose to produce a state-of-the-art overview of the durability of transcatheter aortic valve implantation, by integrating knowledge of the basic science of bioprosthesis degeneration (pathophysiology and biomarkers). After summarizing the new definition of structural valve deterioration, we will present what is known about the pathophysiology of aortic stenosis and bioprosthesis degeneration. Next, we will consider how to identify a population at risk of early degeneration, and how basic science, with the help of biomarkers, could identify and predict structural valve deterioration. Finally, we will present data on the differences in durability of transcatheter aortic valve implantation compared with surgical aortic valve replacement.

KEYWORDS

TAVI;

Durability;

Aortic stenosis;

Biomarkers;

Structural valve deterioration

Abbreviations: AS, aortic stenosis; BVD, bioprosthetic valve dysfunction; BVF, bioprosthetic valve failure; BVT, bioprosthetic valve thrombosis; CI, confidence interval; EAPCI, European Association of Percutaneous Cardiovascular Interventions; PCSK9, proprotein convertase subtilisin/kexin type 9; SAVR, surgical aortic valve replacement; SVD, structural valve deterioration; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve.

Background

Since the description of the first human case [1], performed in Rouen University Hospital on 16 April 2002 by Alain Cribier and colleagues, the number of cases of transcatheter aortic valve implantation (TAVI) has continued to increase steadily. More than 400,000 patients have been implanted worldwide, and approximately 180,000 patients can be considered TAVI candidates in the European Union and North American annually (or even 270,000 if indications for TAVI expand to low-risk patients) [2]. TAVI is now widely accepted by the medical community as one of the major advances in cardiology in the last 20 years.

Originally restricted to high-risk or inoperable patients in the 2012 guidelines [3], there has been an extension of the indication to the intermediate-risk population in the most recent guidelines, based on the results of two large randomized clinical trials (PARTNER 2 and SURTAVI) [4]. Two other trials published recently (PARTNER 3 [5] and EVOLUT LOW RISK [6]) focused on low-risk patients, and indicated that TAVI is non-inferior or even superior in term of clinical outcomes to surgical aortic valve replacement (SAVR).

In cardiac surgery, bioprosthetic aortic valve deterioration is a well-known complication. Because TAVI was initially reserved for elderly or inoperable patients, data on structural valve deterioration (SVD) and durability beyond 5 years are still limited, raising the question of the viability of its extension to low-risk/younger patients with a longer life expectancy.

Recently, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) proposed standardized definitions for bioprosthetic valve dysfunction (BVD) [7].

At the same time, advances in basic science are providing a better understanding of the pathophysiology of the development of aortic stenosis (AS) and BVD [8-10]. New biomarkers have recently been identified, and although not all are currently used in routine clinical practice, they could provide a valuable aid in the management of SVD (transcatheter or surgical).

The aims of this translational review are: (1) to summarize the new standardized definitions of BVD and SVD; (2) to present an inventory of knowledge in terms of the pathophysiology of native AS and bioprosthetic SVD; and (3) to establish current knowledge of TAVI durability, before finishing with BVD biomarkers.

Definitions of BVD and SVD (from guidelines)

BVD is a well-known complication of surgical bioprosthesis. Despite efforts, there is no ideal prosthetic valve substitute as yet. Classically, SVD is defined in terms of survival without reintervention [11]. Unfortunately, this definition considerably underestimates the rate of SVD, because it is considered only in patients with severe SVD, as well as in those with an adequate risk profile allowing redo surgery. In contrast, it may overestimate SVD in cases of reintervention for paravalvular regurgitation, thrombosis or infective endocarditis.

SVD happens more or less quickly, depending on the type of bioprosthetic valve. Using Carpentier-Edwards valves (Edwards Lifesciences, Irvine, CA, USA), Forcillo et al. [12] reported rates of freedom from reoperation of 98 ± 0.2% and 96 ± 1% at 5 and 10 years, respectively, whereas Sénage et al. [13] showed early SVD using Mitroflow valves (Sorin Group, Milan, Italy). Obviously, there was a need for a standardized universal definition of SVD in order to compare surgical and transcatheter heart valve (THV) durability. This becomes particular important in the context of the extension of TAVI to younger patients with a longer life expectancy.

In 2017, the EAPCI, endorsed by the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery [7], proposed a consensus definition, applicable to both transcatheter and surgically implanted bioprosthetic valves. They proposed the term of BVD, encompassing four modes of dysfunction (Fig. 1), all suspected via transthoracic echocardiography: SVD; non-SVD; bioprosthetic valve thrombosis (BVT); and endocarditis.

SVD is probably the most common type of BVD [10], and is characterized by permanent intrinsic changes to the valve (i.e. leaflet tear, calcification, pannus deposition flail, fibrotic leaflet), leading to degeneration and/or dysfunction that, in turn, may result in stenosis or intraprosthetic regurgitation. Two types of SVD are described, and can coexist: morphological SVD and haemodynamic SVD (see Table 1 for definition). Morphological SVD needs at least multidetector computed tomography to be diagnosed, whereas the diagnosis of haemodynamic SVD is based on the change in mean transvalvular aortic gradient from baseline (≤ 30 days after valve implantation) and/or worsening or new central aortic regurgitation by echocardiography. Haemodynamic SVD can be moderate or severe based on mean transaortic gradient and/or with moderate or severe intraprosthetic regurgitation.

Dvir et al. [14] proposed a complementary definition of SVD, with three stages of classification, considering SVD not as a binary categorial variable, but rather as a continuum, each stage being

associated with a specific clinical approach. Stage 1 is defined as morphological leaflet abnormality (i.e. leaflet calcification or sclerosis) without significant haemodynamic changes (mean gradient < 20 mmHg, intravalvular regurgitation < moderate). Stage 2, after thrombosis exclusion, is defined as moderate stenosis (increase in mean gradient of > 10 mmHg from baseline value, with a decrease in valve area) (stage 2S) or moderate intravalvular regurgitation (stage 2R) or 2S and 2R (stage 2RS). Stage 3 is defined as severe stenosis and/or regurgitation.

Bioprosthetic valve failure (BVF) is used when there are clinical implications of BVD. BVF includes any of the following: (1) death probably related to BVD (confirmed by autopsy or by clinical diagnosis of BVD before death); (2) repeated intervention (including valve-in-valve TAVI, paravalvular leak closure or surgery); and (3) severe haemodynamic SVD. BVF can be categorized as definite (autopsy, reintervention, severe haemodynamic SVD) or probable (valve-related death without autopsy), as well as early (≤ 30 days) or late (> 30 days) after transcatheter or surgical valve replacement.

SVD has to be differentiated from BVT. An increase in mean transprosthetic pressure gradient with/or without new onset symptoms or heart failure should alert the physician to the possibility of BVT. Multidetector computed tomography/transoesophageal echocardiography must be performed as soon as possible. If leaflet thickening is detected, anticoagulation treatment should be considered. All patients with BVT should undergo repeat transthoracic echocardiography within 3–6 months. If BVT is excluded, then SVD must be considered.

Nevertheless, these definitions are sometimes imperfect, and attention should be paid to patients with cardiovascular risk factors and co-morbidities, particularly arterial hypertension or any state of hyperflow (i.e. anaemia, hyperthyroidism, etc.). Indeed, hypertensive patients develop subaortic bulge, which creates an acceleration of the flow in the left ventricular flushing chamber, creating false elevation of the transvalvular aortic gradients. Thus, it can be wrongly concluded that there is SVD, hence the importance of orifice areas and index of permeability, which are not part of the definition. Guidelines recommend reassessment of the hypertensive patient with AS when their blood pressure is under control.

Pathophysiology

Aortic stenosis

The normal aortic valve is composed of three leaflets, subdivided into three layers: the fibrosa (aortic side, rich in collagen fibres); the ventricularis (ventricular side, rich in elastin fibres); and the spongiosa (between the two layers, rich in proteoglycans). This architecture confers the valve's biomechanical properties, which are essential to absorb mechanical constraints. Two different types of cells are described: valvular interstitial cells and valvular endothelial cells, which have important crosstalk and modulate the biology of the native valve. Native AS is a frequent disease of the elderly, characterized by progressive calcification and stiffening of leaflets, leading to aortic valve replacement, mainly by biological tissue prostheses. However, surgical bioprostheses can also undergo progressive deterioration over time, with subsequent failure after 10–15 years.

Over the last 15 years, knowledge of the molecular basis of the development of AS has grown considerably. Study of the pathophysiology of native AS has allowed identification of a series of finely regulated molecular mechanisms leading to the development of the calcified valve tissue [8, 10, 15]. Our better understanding of the pathophysiological processes in native AS has, at the same time, clearly contributed to the identification of mechanisms associated with bioprosthetic SVD, given that SVD resembles, to some extent, native AS.

AS has been characterized as a fibrocalcific disease with an excess of extracellular matrix and the development of mineralized nodules on the aortic valve, which lead to the obstruction of the left ventricular outflow tract. Several environmental risk factors, such as hypertension and obesity/metabolic syndrome, have been associated with the development and progression of the disease [16-19]. The similarities reported between risk factors and pathophysiological processes leading to atherosclerosis and AS support the idea that AS is an atherosclerosis-like disease [19]; hypertension, diabetes, renal disease, dyslipidaemia, lipoprotein accumulation and oxidation and local inflammation are reported to be involved in the development and progression of both pathologies, suggesting that the knowledge of and therapeutic options available for atherosclerosis could be directly transposed to AS. However, important differences between these two pathologies have also been highlighted, and have challenged this conclusion: only around 40% of patients with AS present concomitant atherosclerosis, and statin treatment failed to reduce the progression of AS in three large randomized clinical trials [18, 20, 21]. These findings suggest that AS should not be considered only as an expression of atherosclerosis, and that specific pathophysiological processes, or their regulation, are involved in the development and progression of AS.

Many different pathophysiological processes have been highlighted as part of the development of AS [8, 10, 15]. Endothelial dysfunction, lipid deposition, inflammatory infiltrate, osteogenic programme activation, neovascularization and engraftment into the valve of circulating haematopoietic stem cells are regarded as the main factors involved in the development of native AS.

Endothelial dysfunction increases leucocyte adhesion and the permeability of the valve tissue to lipids and inflammatory cells, which will, in turn, promote the osteogenic programme in the valve [22]. In addition, the crosstalk between valvular endothelial cells and valvular interstitial cells, which is described as maintaining valve homeostasis, could be significantly disturbed, and lead to the activation of procalcifying pathways [23]. Even if the underlying molecular mechanisms remain largely unknown, recent studies have described a two-way valvular endothelial cell-valvular interstitial cell communication that, in pathological conditions such as development of AS, can lead to the activation of specific cell functions and further promote valve calcification [23].

Lipid deposition and its impact on the activation of osteoblastic programme is certainly the factor that has been studied most extensively. Indeed, the first single-nucleotide polymorphism (rc10455872), identified in a large genome-wide association study, was located in the *LPA* gene, coding for circulating level of lipoprotein(a) [24]. Lipoprotein(a) is a highly heritable factor, with up to 90% of its variance explained by genetic predispositions, and with low influence of age and environmental factors on its circulating level [25]. Since the publication of this first genetic association study, several reports have confirmed the link between lipoprotein(a) and the development of AS [26-29].

Further studies have provided compelling data supporting the relationship between lipids and AS. Oxidized low-density lipoprotein and oxidized phospholipids, which are mainly carried in plasma by lipoprotein(a), are key factors in the pathophysiological process leading to calcification of the valve [30, 31]. Oxidized phospholipids, which are a trigger for inflammation and recruitment of macrophages, are used as a substrate by lipoprotein-associated phospholipase A2 (transported by lipoprotein(a), but also secreted by macrophages) to generate lysophosphatidylcholine, a factor promoting inflammation and a procalcific programme via autotaxin action [29, 32-35]. Indeed, autotaxin, which is also enriched in lipoprotein(a), and is secreted by valvular interstitial cells in response to tumour necrosis factor alpha, promotes inflammation and, importantly, hydrolyses lysophosphatidylcholine into lysophosphatidic acid, a proinflammatory factor directly involved in the development of ectopic

calcification. Lipid effects are also exacerbated by the increased expression of byglycan, a promoter of lipid retention in the aortic valve [36, 37]. These findings highlight a potentially interesting means of treating AS, by targeting the lipoprotein(a)/oxidized phospholipids/autotaxin pathway. For this purpose, a new class of drug that enables reduction of lipoprotein(a) plasma concentration by up to 90% is under development [38]. Finally, a recent study that will need further validation suggests that proprotein convertase subtilisin/kexin type 9 (PCSK9) could also be a potential target to treat AS [39].

Inflammation is highly present in calcified aortic valve; the inflammatory infiltrates have been associated with extracellular matrix remodelling and osteochondrogenic metaplasia [40]. The reported high expression in diseased tissue of tumour necrosis factor alpha, a proinflammatory cytokine mainly produced by macrophages to regulate immune response, promotes an inflammatory state that exacerbates calcification processes as well as enhances local production of autotaxin [41, 42]. In response to the high level of inflammation, metalloproteinase 2 and metalloproteinase 9 are expressed, and participate in the extracellular matrix remodelling and angiogenesis [43]. Circulating factors, such as haematopoietic stem cells and progenitor cells, have been described to affect valve biology in AS; engraftment of these cells into the valve may help to regenerate tissue, but these cells are also more prone to mineralize and differentiate into proinflammatory/procalcifying cells [44].

The involvement of these pathophysiological pathways related to extracellular matrix remodelling and profibrotic processes, inflammation and mineralization, in combination with lipid effects, were also highlighted recently in a genome-wide association study that identified new loci associated with AVS. *PALMD*, *IL6*, *ALP* and *NAV1* genes were identified, and provide genetic confirmation of the involvement and interrelationship of these pathways in promoting remodelling and mineralization of the aortic valve [45]. However, the pathophysiological mechanisms leading to AS remain incompletely understood, and further studies are needed to decipher the different pathways involved in this process.

Bioprosthetic SVD

Bioprosthetic heart valves are used widely nowadays for the treatment of severe symptomatic AS. However, as encountered in the native aortic valve, this biological tissue is also prone to degenerate, leading to prosthesis dysfunction and the need for a redo intervention [46, 47].

The leading mechanisms of bioprosthetic SVD have been studied intensively, and it has been highlighted that, even if the molecular mechanisms involved in native AS and SVD are not completely substitutable, there are many similarities; indeed, the leading process in SVD is also described as fibrocalcification of the prosthetic valve tissue [46, 47]. In addition, thrombosis and immune rejection have been described as participating processes in SVD.

Fibrocalcification processes and mechanical stress leading to SVD

Several mechanisms have been described as potential factors to explain SVD. Cardiovascular risk factors, including metabolic abnormalities (i.e. metabolic syndrome, diabetes, dyslipidaemia, phosphocalcic metabolism dysregulation, renal failure, hyperparathyroidism) and increased mechanical stress (i.e. hypertension, patient-prosthesis mismatch, small-sized prosthesis), have been associated with SVD [9, 48-55]. The majority of them are modifiable and, in patients undergoing aortic valve replacement with a bioprosthesis, these risk factors should be treated aggressively to reduce SVD.

Active mechanisms have been reported, and encompass inflammation, insulin-resistance and lipid-mediated mechanisms – processes leading to bioprosthesis calcification and further SVD [56-58]. As observed in native AS, lipid infiltration and inflammation have been reported in bioprosthetic tissue; oxidized low-density lipoproteins are present, and are well described as a trigger for valve calcification [57, 58]. More recently, recruitment of progenitor cells and dendritic cells, which are prone to osteoblastic differentiation, has also been observed in explanted bioprosthesis valve tissue [58, 59]. All these mechanisms, which resemble those reported in native AS, lead to the development of tissue calcification that will, in turn, weaken bioprosthesis valve leaflets and cause clinically relevant stenosis and/or regurgitation.

Valve surgery or TAVI are performed in patients with multiple concomitant co-morbidities, especially hypertension, which is one of the most prevalent co-morbidities, and can significantly increase the mechanical stress imposed on the bioprosthetic leaflets [9]. In the same vein, aortic valve surgery using a surgical bioprosthesis or TAVI can be associated with postoperative patient-prothesis mismatch, which is also known to significantly increase the mechanical stress on the leaflets [9, 46, 50]. This increased stress has been linked to the development of SVD, and should be systematically prevented or treated aggressively following valve implantation.

Glutaraldehyde-based approaches and SVD

Another aspect associated with SVD can be related to the fixation process used to manufacture and store bioprostheses. Indeed, the glutaraldehyde-based fixation of biological tissue, used in order to mask the antigen and avoid immune rejection, exacerbates the passive calcification process [60]. Moreover, it has been reported that the glutaraldehyde fixation process does not completely eliminate the antigenicity of bioprosthetic tissue; hence the immune response can take place on the bioprosthesis, which in turn will lead to infiltration of macrophages, monocytes and T cells, and the development of local inflammation [60, 61]. To avoid this issue, manufacturers are working on alternatives, such as decellularization and/or anticalcification pretreatment, to reduce the incidence of bioprosthesis failure.

Bioprosthetic thrombosis and SVD

Valve thrombosis is another issue potentially related to SVD, especially in the early postprocedural phase, with relative high frequency in THV (one in six patients) when including subclinical and clinical significant expression [62, 63]. In both cases, thrombosis may induce local inflammation that, in turn, will participate in the implementation of the fibrocalcifying process, leading to future valve dysfunction [63]. Interestingly, lipoproteins – particularly lipoprotein(a) – are recognized for their prothrombotic properties, and thus could have a double impact on SVD [64]: participation in the implementation and persistence of the lipid/inflammatory mediated processes; and development of thrombosis.

Identification of SVD

Identifying the population at risk

Salaun et al. [54] identified several variables associated with haemodynamic SVD following SAVR. After successive adjustment for sex, age and time interval since SAVR, leaflet calcification, insulin resistance, lipoprotein-associated phospholipase A2 activity and a high level of PCSK9 were significantly associated with haemodynamic SVD. In another publication [55], they also identified two types of haemodynamic SVD risk factors after SAVR: early (≤ 5 years) risk factors (diabetes, active smoking, renal insufficiency, baseline postoperative mean gradient ≥ 15 mmHg, transprosthetic regurgitation ≥ mild, type of valve (stented versus stentless) and severe patient-prothesis mismatch);

or late (> 5 years) risk factors (female sex, warfarin use, stented valve and severe patient-prothesis mismatch).

In this study, haemodynamic SVD was associated with a 2.2-fold higher mortality rate after multivariable adjustment for confounders. At the same time, in 2018, Del Trigo et al. [62] showed that the absence of anticoagulation at hospital discharge was associated with higher rates of haemodynamic SVD during follow-up ($P = 0.002$), but was not associated with higher rates of cardiovascular death or stroke. Finally, results of studies by Salaun et al. and Del Trigo et al. suggest that anticoagulation could be beneficial in the early phase by preventing valve thrombosis, but could then be associated with prosthetic valve calcification in the long-term user [55, 62].

This result was confirmed recently by Overtchouk et al. [65], who found that anticoagulation at discharge was associated with a lower rate of BVD after 3 years (adjusted odds ratio 0.54, 95% confidence interval [CI] 0.35–0.82; $P = 0.005$). Sellers et al. [66] provided additional information regarding the use of anticoagulation in the early phase after implantation to prevent SVD. After evaluation of 23 explanted THVs, they demonstrated that there was a link between valve thrombosis and SVD. In the absence of anticoagulation, a thrombus is formed, then endothelial hyperplasia, fibrosis, tissue remodelling with proteinase expression and finally calcification, suggesting a link between thrombosis and subsequent SVD.

Durand et al. [67] observed that valve size < 26 mm was also a predictive factor for SVD. This is consistent with the analysis of Del Trigo et al. [68] who reported that the use of a 23 mm valve was an independent predictor of haemodynamic SVD. They also found that the valve-in-valve procedure and a greater body mass index were associated with an increased risk of SVD. For Rodriguez-Gabella et al. [47], body mass index, dyslipidaemia, persistent left ventricular hypertrophy and patient-prothesis mismatch were predictors of SVD.

Several studies have reported that age at time of surgical valve implantation is a major risk factor for bioprosthesis degeneration [11, 12, 47]. This is probably based on the different rate of referral for redo surgery that infers a bias in the analysis of this specific endpoint by using survival without reintervention as a definition of SVD; young and/or low-risk patients are referred and undergo the redo surgery.

Concerning sex differences, as Rodriguez-Gabella et al. reported [47], there are contradictory data; some studies have found male sex to be associated with accelerated SVD whereas others have found female sex to be associated with accelerated SVD.

Biomarkers: From basic research to daily clinical practice

In the context of bioprosthesis degeneration, recent data have highlighted the potential benefit of some biomarkers.

As previously discussed, clinical risk factors have been associated with SVD [50-55]; some are not modifiable (i.e. age and female sex), and thus can only be taken into account for management of patients and decision making, but several other clinical factors can be regulated. Indeed, hypertension, metabolic syndrome, insulin-resistance, type II diabetes and chronic renal failure can be modulated by drug or lifestyle modification, and an aggressive approach targeting these risk factors, associated with close follow-up of patients, could be implemented to reduce the incidence of SVD.

Lipid markers – lipoprotein(a)-oxidized phospholipids-autotaxin pathway and PCSK9 protein – as well as those related to insulin-resistance, such as the homeostatic model assessment of insulin resistance (HOMA index), can be used as circulating biomarkers, and provide interesting data in the context of SVD, as highlighted in recent publications [51-54, 57, 58]. Similarly, CD14 – a marker of macrophage activation that is increased in patients with proinflammatory state, such as those with metabolic syndrome – has recently been associated with a higher rate of SVD [69]. Finally, biomarkers of phosphocalcic metabolism or renal function – such as the calcium-phosphate product, the level of parathyroid hormone or creatinine clearance – are also associated with the development of SVD [70]. Although confirmatory results are needed to reinforce the usefulness of these biomarkers, and then to promote their generalization into the clinic, this approach, based on identifying circulating biomarkers, can help to stratify the risk of SVD development and, potentially, affect patient management and the decision-making process. Further efforts should be made to enhance the validation of these biomarkers, as well as to identify new ones that will help to improve management and the decision-making process for these patients.

Given the exponential growth of imaging availability and its use in the field of valvular diseases, imaging biomarkers have emerged in the literature, and could significantly impact management and decision making for patients who undergo SAVR or TAVI. Echocardiography is the first-line imaging

modality, and provides information on bioprosthetic function, as well as on the myocardium [71, 72]. In past decades, evidence for the use of new imaging modalities has been published to refine diagnosis, management and therapeutic decisions: multidetector computed tomography, positron emission tomography and cardiac magnetic resonance imaging are used increasingly in this population. Multidetector computed tomography provides a quantitative assessment of calcium content – one of the most reliable indices of morphological leaflet damage in the bioprosthetic valve [71]. Positron emission tomography scanning has recently emerged as a marker of active calcification; ^{18}F-fluorodeoxyglucose and ^{18}F-sodium fluoride are widely available, and can be used to assess valve or prosthesis inflammation and microcalcification, respectively [73]. Finally, cardiac magnetic resonance imaging offers the opportunity to assess concomitant myocardial remodelling and/or dysfunction; it provides indices of left ventricular mass and function, but also reveals the presence of left ventricular fibrosis (i.e. replacement or interstitial fibrosis assessed by T1 mapping) [71]. All of these indices could be used for risk stratification and could modify patient management.

Comparison of durability

TAVI versus SAVR

Different types of biological prosthetic valves have been used for several decades, and have been improved over time to extend, at least in part, their durability. In this regard, stented versus stentless and porcine versus bovine pericardium prostheses provide different benefits/risks (i.e. superior effective orifice area, reduced transprosthetic gradient, greater left ventricular mass regression with stentless compared with stented bioprosthesis [46, 74]). More recently, the THV has emerged as a new biological prosthesis.

Several large series evaluating SVD have already been published, including different types of bioprosthesis and based on various definitions (usually survival without reintervention). Johnston et al. [11] evaluated the Carpentier-Edwards PERIMOUNT bioprosthesis (Edwards Lifesciences, Irvine CA, USA) (n = 12,569), implanted between June 1982 and January 2011, and reported rates of freedom from SVD (freedom from reintervention) of 98.1% and 85% at 10 and 20 years, respectively. Bourguignon et al. [75], with the same bioprosthesis (n = 2758), reported rates of freedom from redo surgery of 79 ± 2% and 49 ± 5% at 15 and 20 years, respectively, with an expected valve durability of 19.7 years in the entire cohort. All these results show that the long-term durability of surgical

bioprostheses is excellent. In contrast, Sénage et al. [13] reported a higher rate of SVD, especially for small annulus sizes (SVD occurrence was 20% and 5% at 5 years for sizes 19 mm and 21 mm, respectively), and a 5-year SVD-free survival rate of 91.6% using the Mitroflow bioprosthesis.

Surgical and transcatheter bioprostheses are different in several aspects. Unlike with SAVR, native AS remains in place when implanting a THV; thus, it modifies valve leaflet geometry, and may cause valve distortion and turbulence, which can affect haemodynamics and accelerate SVD. Moreover, mechanical stresses associated with sample preparation and delivery of a THV, such as crimping the valve tissue and/or performing postdilatation, can create microscopic tissue lesions that can further promote degenerative processes. Dvir et al. [14] reported that the first-generation of THVs used porcine pericardium with no established long-term durability. However, this has changed with the latest-generation valves (bovine pericardium, as with the Carpentier-Edwards PERIMOUNT valve). Direct comparisons between SAVR and TAVI, and data on TAVI durability beyond 5 years are still limited, mainly because of the relatively recent use of TAVI (first implantation in 2002) and the indications limited to compassionate patients in the early years. Nevertheless, several registries are providing important data (Table 2).

From the PARTNER 1 trial (balloon-expandable valve versus surgery) [76], Mack et al. reported a similar risk of death at 5 years for SAVR and TAVI (67.8% versus 62.4%, hazard ratio 1.02, 95% CI 0.86–1.24; $P = 0.76$), with no SVD requiring redo intervention in either group. Concerning the self-expandable valve (CoreValve™; Medtronic, Minneapolis, MN, USA), Barbanti et al. [77] observed a rate of 1.4% of significant SVD according to Valve Academic Research Consortium 1 (VARC-1) criteria [78]. Toggweiler et al. [79] reported a rate of SVD of 3.4% at 5 years. In the FRANCE-2 registry [80], providing the greatest amount of long-term data in a high-risk population, the 5-year rates of severe SVD and moderate/severe SVD were 2.5% and 13.3%, respectively.

Data beyond 5 years are sparse. In 2018, Eltchaninoff et al. [81], from the pioneer TAVI centre, reported a series of 378 patients implanted with a balloon-expandable device from April 2002 to September 2012. The incidences of SVD (using the new definitions) and BVF at 8 years were low: 3.2% (95% CI 1.45–6.11) and 0.58% (95% CI 0.15–2.75), respectively. A German series of 300 patients [82] showed, after 7 years, a rate of SVD (EAPCI definitions) of 14.9% (CoreValve 11.8% vs SAPIEN [Edwards Lifesciences, Irvine, CA, USA] 22.6%; $P = 0.01$), while Holy et al. [83], in 152 patients who had undergone self-expandable valve implantation, did not report any evidence of SVD.

A multicentre (five centres) French study by Durand et al., which included consecutive patients with at least 5 years of follow-up available, who underwent TAVI from April 2002 to December 2011 (83.7% balloon-expandable valves) was published recently: BVF occurred in 19 patients (7-year cumulative incidence of 1.9% (95% CI 1.4–2.4%), SVD occurred in 49 patients (7-year cumulative incidences of moderate and severe SVD of 7.0% and 4.2%, respectively), with no significant difference between balloon- and self-expandable prostheses [67]. The survival bias associated with these analyses remains the most important limitation to characterization of the long-term durability of TAVI.

The UK TAVI Trial [84], including 241 patients implanted from 2007 to 2011 (149 self-expandable valves, 80 balloon-expandable valves), showed excellent long-term THV function. Between 5 and 10 years after implantation, 91% remained free of SVD, with only one case (0.4%) of severe SVD at 5.3 years after implantation, and 21 cases (8.7%) of moderate SVD (at a mean of 6.1 years after implantation) – 12 (57%) as a result of aortic regurgitation and nine (43%) as a result of restenosis.

The NOTION trial (n = 139) is the first and only study to provide comparative data on bioprosthetic valve durability from a randomized clinical trial in patients at low surgical risk of mortality. The analysis at 6 years [85] (all-comer patients with severe AS and a lower surgical risk of mortality randomized 1:1 to TAVI [n = 139] or SAVR [n = 135] in three centres in Denmark and Sweden) showed that the rate of SVD was higher with SAVR than TAVI (24.0% vs 4.8%; $P < 0.001$), with similar rates of all-cause mortality (42.5% for TAVI vs 37.7% for SAVR; $P = 0.58$) and no differences in terms of non-SVD (57.8% vs 54.0%; $P = 0.52$) and endocarditis (5.9% vs 5.8%; $P = 0.95$).

Further durability studies up to 10 years are needed to support the mid-term/long-term results. This will be done in the context of current registries, such as the EAPCI registry and the STOP-AS RHU (Search Treatment and Improve Outcome of Patients with Aortic Stenosis, Recherche Hospitalo-Universitaire) French registry, and with the planned 10-year follow-up of low-risk patients included in the “low-risk” trials.

Perspectives: TAVI in low-risk patients

The recently published PARTNER 3 [5] and EVOLUT LOW RISK [6] trials have demonstrated that TAVI can be considered in low-risk patients.

In PARTNER 3 [5], using a balloon-expandable valve (n = 1000), the primary composite endpoint (death, stroke and rehospitalization at 1 year) was significantly lower in the TAVI group than in the

surgery group (8.5% vs 15.1%; $P < 0.001$ for non-inferiority and $P = 0.001$ for superiority). Popma et al. [6], with a self-expanding valve, showed that the TAVI and SAVR groups were similar at 12 months.

In the context of extending the indication of TAVI to patients at lower surgical risk and those who are younger, the long-term durability of transcatheter aortic bioprosthetic valves is a major issue. The question of percutaneous valve durability in a low-risk population beyond 10 years remains to be evaluated. Continuous long-term monitoring of patients enrolled in the ongoing study registries and clinical trials will provide this missing and mandatory information.

Conclusions

Even if current data do not give cause for alarm compared with surgical valves, the durability of transcatheter aortic valves beyond 20 years in low-risk patients is still unknown. The mechanisms associated with deterioration of these valves are complex and interrelated. Recent advances in and development of our knowledge will contribute to reduction of the occurrence of these important issues. Even if they are not used in daily clinical practice, circulating clinical and imaging biomarkers have been studied extensively, and participate actively in improving diagnosis, management and the decision-making process for patients with SVD.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Causes of bioprosthetic valve dysfunction, from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) 2017 consensus. TAVI: transcatheter aortic valve implantation.

Central illustration. Transcatheter aortic valve implantation: deterioration biomarkers, pathophysiology and data durability. BVT: bioprosthetic valve thrombosis; ^{18}FDG: ^{18}F-fluorodeoxyglucose; HOMA index: homeostatic model assessment of insulin resistance; Lp(a): lipoprotein(a); MDCT: multidetector computed tomography; PCSK9: proprotein convertase subtilisin/kexin type 9; PET-CT: positron emission tomography; computed tomography; SVD: structural valve deterioration; TAVI: transcatheter aortic valve implantation; TTE: transthoracic echocardiography; y: years.

Table 1 European consensus[a] definition of the two types of structural valve deterioration.

Morphological[b] SVD (any of the following):	Leaflet integrity abnormality (i.e. torn or flail causing intraframe regurgitation)
	Leaflet structure abnormality (i.e. pathological thickening and/or calcification causing valvular stenosis of central regurgitation)
	Leaflet function abnormality (i.e. impaired mobility resulting in stenosis and/or central regurgitation)
	Strut/frame abnormality (i.e. fracture)
Haemodynamic[b] SVD	
Moderate haemodynamic SVD (any of the following):	Mean transprosthetic gradient ≥ 20 mmHg and < 40 mmHg
	Mean transprosthetic gradient ≥ 10 and < 20 mmHg change from baseline
	Moderate intraprosthetic aortic regurgitation, new or worsening > 1+/4+ from baseline
Severe haemodynamic SVD:	Mean gradient ≥ 40 mmHg and/or ≥ 20 mmHg change from baseline
	and/or severe new or worsening aortic regurgitation (> 2+/4+) from baseline

SVD: structural valve deterioration

[a] European Association of Percutaneous Cardiovascular Interventions (EAPCI)/European Association for Cardio-Thoracic Surgery (EACTS).

[b] Both morphological and haemodynamic SVD can be found together.

Table 2 Transcatheter aortic valve implantation durability registries at 5 years and beyond 5 years.

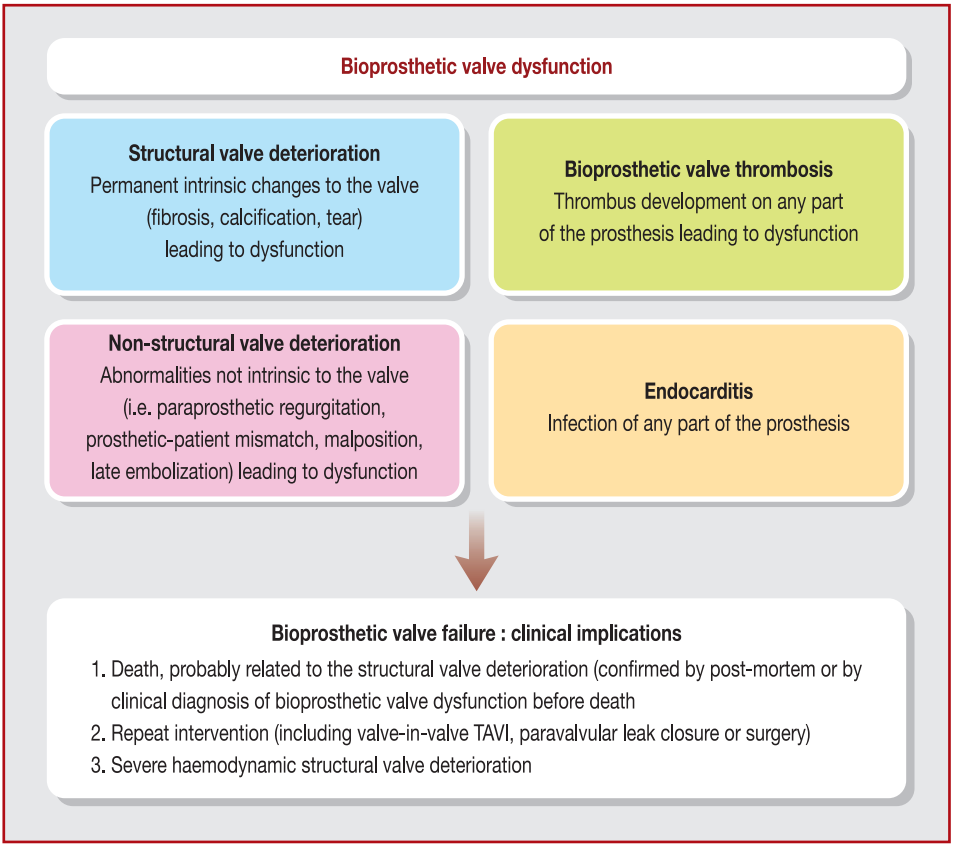
Study reference	*n*	Type of valve	Type of patients	Median follow-up	SVD definition	Cumulative incidence of SVD
Durability at 5 years						
Mack et al. 2015 [76]	348	Balloon-expandable	High-risk	3.14 years	Surgical valve replacement required	0%
Barbanti et al. 2015 [77]	353	Self-expandable	High-risk	3.9 years	VARC-1[a]	1.4%
Toggweiler et al. 2013 [79]	88	Balloon-expandable	High-risk	-	VARC-1[a]	3.4%
Didier et al. 2018 [80]	4201	Balloon- or self-expandable	High-risk	-	EAPCI/EACTS[b]	Severe, 2.5%; moderate, 13.3%
Durability beyond 5 years						
Eltchaninoff et al. 2018 [81]	378	Balloon- or self-expandable	High-risk	-	EAPCI/EACTS[b]	3.2% at 8 years
Durand et al. 2019 [67]	1264	Balloon- (83.7%) or self-expandable	High-risk	3.9 years	EAPCI/EACTS[b]	At 7 years: moderate, 7.0%; severe, 11.2%
Deutsch et al. 2018 [82]	300	Balloon- or self-expandable	High-risk	-	EAPCI/EACTS[b]	14.9% at 7 years
Holy et al. 2018 [83]	152	Self-expandable	High-risk	-	Severe SVD: mean gradient ≥ 40 or increase of 20 mmHg from baseline or severe	0% at 8 years

					intraprosthetic AR or BVF leading to death or reintervention	
Blackman et al. 2019 [84]	241	Balloon- or self-expandable	High-risk	5.8 years	EAPCI/EACTS[b]	Severe, 0.4% at 5.3 years; moderate, 8.7% (mean 6.1 years)
Sondergaard et al. 2019 [85]	139	Self-expandable	All-comer	-	Moderate/severe SVD: mean gradient ≥ 20 or increase of 10 mmHg from 3 months postprocedure or ≥ mild intraprosthetic AR	4.8% at 6 years

AR: aortic regurgitation; BVF: bioprosthetic valve failure; EACTS: European Association for Cardio-Thoracic Surgery; EAPCI: European Association of Percutaneous Cardiovascular Intervention; SVD: structural valve deterioration; TAVI: transcatheter aortic valve implantation; VARC: Valve Academic Research Consortium.

[a] VARC-1 definition of SVD.

[b] For EAPCI/EACTS definition of SVD, see Table 1.


Bioprosthetic valve dysfunction
Structural valve deterioration
Permanent intrinsic changes to the valve (fibrosis, calcification, tear) leading to dysfunction
Bioprosthetic valve thrombosis
Thrombus development on any part of the prosthesis leading to dysfunction
Non-structural valve deterioration
Abnormalities not intrinsic to the valve (i.e. paraprosthetic regurgitation, prosthetic-patient mismatch, malposition, late embolization) leading to dysfunction
Endocarditis
Infection of any part of the prosthesis
Bioprosthetic valve failure : clinical implications
1. Death, probably related to the structural valve deterioration (confirmed by post-mortem or by clinical diagnosis of bioprosthetic valve dysfunction before death
2. Repeat intervention (including valve-in-valve TAVI, paravalvular leak closure or surgery)
3. Severe haemodynamic structural valve deterioration

Pathophysiology of bioprosthesis valve deterioration
"Similitudes with native valve deterioration and differencies"

Fibrocalcification of the prosthesis tissue
- Traditional cardiovascular risk factors
- Phosphocalcic metabolism dysregulation
- Increased mechanical stresses (hypertension, mismatch, small sizing)
- Glutaraldehyde-based fixation : passive calcification with circulating phospholipids and calcium ions → collagen fixation : increase of rigidity

Lipid inflammatory-mediated process
- Macrophage infiltration, monocytes, T-cells
- Lp(a), oxidized phospholipids, PCSK9
- Osteoblastic differentiation

Valve thrombosis
- Increase local inflammation and fibrocalcifying process
- Lp(a) : pro-thrombosis property

5-years durability **
- Mack, MJ 0%
- Barbanti, M 1.4%
- Toggweiler, S 3.4%
- Didier, R 2.5%

Beyond 5-years durability **
- Eltchaninoff, H 3.2% at 8y
- Durand, E 4.2% at 7y
- Deutsch, MA 14.9% at 7y
- Holy, EM 0% at 8y
- Sondergaard, L 4.8% at 6y

Perspectives
Durability beyond 10-15 years and in low-risk patients ?
Decellularisation and/or anticalcification pre-treatment to reduce bioprosthesis failure ?
TAVI extension to low-risk patients in guidelines ?

TAVI indicated by heart team

TTE at discharge, 30 days, then yearly : structural valve deterioration (SVD) ? *

Date of implantation — 5 years — > 10 years

Bioprosthesis deterioration biomarkers

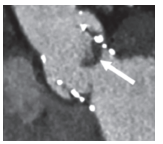
Circulating
- Lipids
- Renal insufficiency
- HOMA index
- Calcemia level
- Parathyroid hormone level
- CD14a level

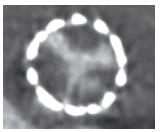
Imaging
- Echocardiography
- MDCT
- PET-CT with ^{18}FDG
- Cardiac magnetic resonance

Identify a population at risk of early deterioration
- Dysmetabolic profile, insulin resistance
- Diabetes
- Renal insufficiency
- Age ? Female gender ?
- No anticoagulation at discharge, then long-term antcoagulation
- Valve sizing < 23-26 mm

SVD suspected by TTE during follow-up *

Bioprosthesis valve thrombosis (BVT) ?
Consider MDCT as soon as possible





BVT confirmed
Consider anticoagulation and repeated TTE

BVT excluded and SVD confirmed
Consider valve-in-valve TAVI

** Severe SVD defined by mean aortic gradient ≥ 40 mmHg and/or ≥ 20 mmHg change from baseline and/or severe new or worsening aortic regurgitation (> 2+) from baseline.*

*** SVD cumulative incidence.*