Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

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Introduction

Despite continuing efforts during the last decades, there is no 'ideal prosthetic valve substitute'. Every valve prosthesis invokes new pathophysiological processes, including the risks of thromboembolism, prosthetic endocarditis, and structural valve deterioration (SVD) or non-structural valve deterioration with consequent need for reintervention (*Figure 1*). Bioprostheses are now increasingly used in preference to mechanical valves in the aortic position but valve dysfunction may occur over time. The literature concerning surgical prostheses has taught us that bioprosthetic valve dysfunction is a complex phenomenon whose understanding requires more than the reporting of reintervention. Further research must encompass biological, pathological and haemodynamic mechanisms, use of contemporary non-invasive imaging, evaluation of the true incidence while avoiding methodological pitfalls, and identification of clinical, technical, and prosthesis-specific predictors.

Since introduction in 2002 and broader clinical use in 2007, penetration of transcatheter aortic valve implantation (TAVI) has grown exponentially as a result of accruing evidence demonstrating safety and efficacy, and reduced invasiveness compared with surgery. TAVI is now the recommended therapy in elderly patients with aortic stenosis who are inoperable or at increased surgical risk[1] and recent evidence has demonstrated at least its equivalence to surgery in intermediate and high-risk cohorts.[2–4] However, our knowledge concerning the clinical outcomes of TAVI beyond 5 years is still limited. Although SVD is likely to be the main mechanism of bioprosthetic valve dysfunction in the longer term, definitions of SVD vary and follow-up studies are scarce. While it is possible to draw lessons from longer term experience with surgical bioprostheses, there are fundamental differences between TAVI and surgical aortic valve replacement (SAVR) (i.e. remaining valve calcification, mechanical stress, crimping of the valve tissue, valve leaflet geometry, balloon expansion or dilation, differences in haemodynamic profile, and patient-prosthesis mismatch), which may impact on the natural history of SVD (see Supplementary material online, Appendix). Critically, extended knowledge of the durability of TAVI is essential as we enter the time (>5 years after implantation) when SVD starts to occur in surgical bioprostheses. This knowledge assumes even greater importance as we consider expanding the indications for TAVI to lower risk and younger patients. As such, standardizing the definitions of valve- and patient-oriented durability outcomes is of paramount importance to enable objective evaluation of existing and novel TAVI prostheses, and their comparative efficacy vs. SAVR.

In this context, the European Association of Percutaneous Cardiovascular Intervention (EAPCI) determined that improved characterization of long-term TAVI outcomes was timely. Two face-to-face meetings (September 2016, London; January 2017, Frankfurt) involving members of the EAPCI, the European Society of Cardiology (ESC), and the European Association for Cardio-Thoracic Surgery (EACTS) representing interventional cardiology, clinical cardiology, imaging and surgery, provided much of the discussion to inform the present document. Herein, we present the available evidence on TAVI SVD, addressed in terms of existing definitions, predictors, and

Figure 1 Causes of bioprosthetic valve dysfunction.
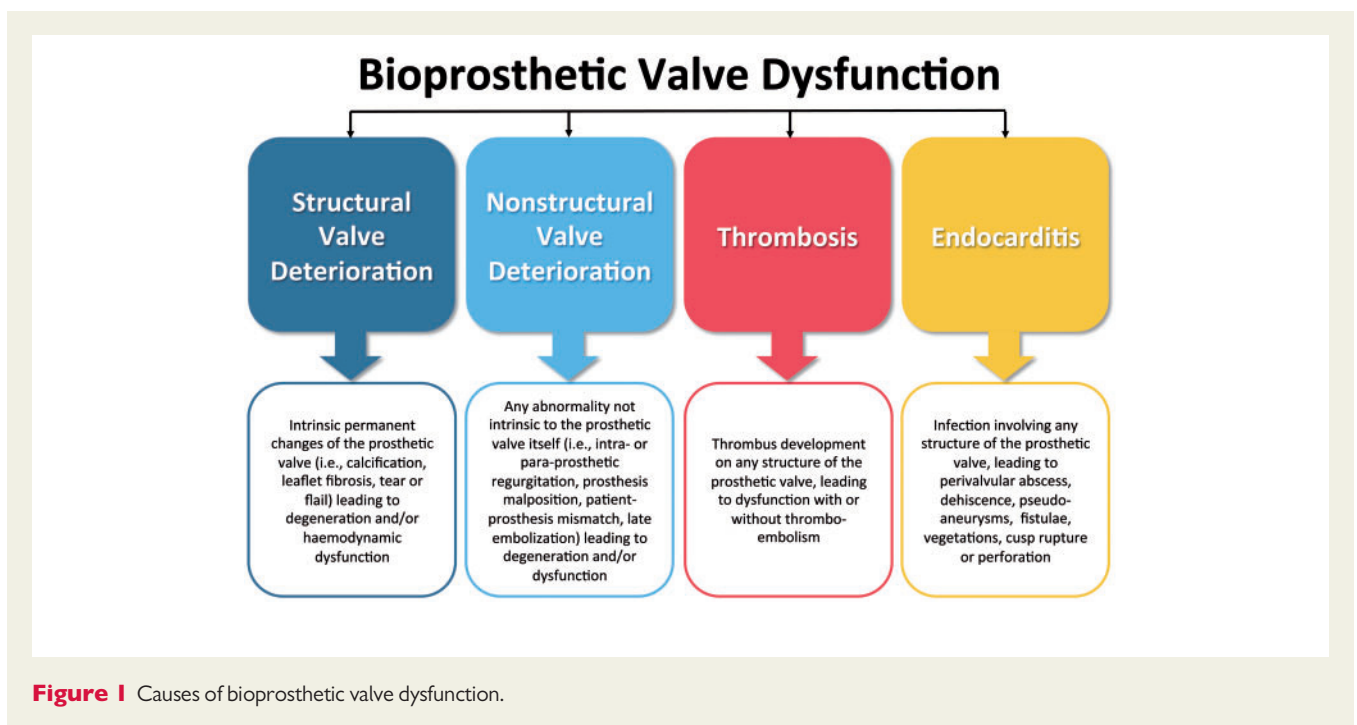
detection. In parallel, we present a standardized definition of SVD and a new patient-oriented clinical end point named bioprosthetic valve failure (BVF) for use in future studies, which aims to capture the clinically relevant manifestations and consequences of SVD or other forms of bioprosthetic valve dysfunction. This effort precedes a registry initiated within the ESC European Observational Registries Programme (EORP) which will evaluate the incidence, presentation, mode, and timing of bioprosthetic valve dysfunction in a contemporary real-world setting. The ultimate goals of this multidisciplinary collaboration are to improve the characterization of SVD and BVF in line with similar ongoing efforts by the Valve Academic Research Consortium (VARC) 3 and optimize the future utilization of TAVI.

Existing definitions of structural valve deterioration

Survival without valve reintervention or explant for SVD is an outcome still used by some published series to assess the durability of surgical bioprostheses.[5] However, surgical guidelines for event reporting after cardiac valve interventions have not supported this approach since 2008, and stipulate that SVD should also be defined by clinically detectable measures other than the need for reoperation for a failing bioprosthesis (i.e. using echocardiographic criteria).[6] In 2009, Zoghbi *et al.*[7] published a series of recommendations for the evaluation of prosthetic valves using echocardiography and Doppler ultrasound. Possible stenosis was defined as peak prosthetic aortic jet velocity 3–4 m/s, mean gradient 20–35 mmHg, and effective orifice area 0.8–1.2 cm^2. Significant stenosis was defined as peak prosthetic aortic jet velocity >4 m/s, mean gradient >35 mmHg, and effective orifice area <0.8 cm^2. The 2012 ESC guidelines, written in collaboration with the EACTS, recommend annual echocardiography beyond the first 5 years following bioprosthetic valve implantation (and earlier in young patients) to detect early evidence of 'SVD, leaflet stiffening, calcification, reduced effective orifice area, and/or regurgitation'.[1] Based on these guidelines, the transprosthetic gradients should be interpreted in comparison with the baseline values. This requires an early postoperative assessment to set up a reference point for future investigations and to detect important conditions such as patient-prosthesis mismatch and left ventricular dysfunction. Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient or severe regurgitation (Class I, Level of Evidence C) and should be considered in asymptomatic patients with significant bioprosthetic valve dysfunction, provided they remain at low-surgical risk (Class IIa, Level of Evidence C). The VARC-2 recommendations also suggest echocardiography as the principal imaging modality for assessment of bioprosthetic valve function immediately before initial hospital discharge (to establish baseline parameters) and at 6 months, 1 year, and annually thereafter.[8] VARC-2 defines SVD as (i) valve-related dysfunction (mean aortic gradient ≥20 mmHg, effective orifice area ≤0.9–1.1 cm^2, and/or dimensionless valve index <0.35, and/or moderate or severe prosthetic valve regurgitation) or (ii) need for a repeat procedure (TAVI or SAVR). Lancellotti *et al.*[9] suggested incorporating an increase in mean gradient during stress echocardiography or at follow-up (possible obstruction 10–19 mmHg; significant obstruction ≥20 mmHg). In a recent surgical series, Bourguignon *et al.*[10] defined SVD using strict echocardiographic

criteria independent of symptomatic status, including severe aortic stenosis (mean transvalvular gradient >40 mmHg) and severe aortic regurgitation (effective regurgitant orifice area >0.30 cm^2, vena contracta >0.6 cm). Of note, this definition relies on the systematic implementation, recording and reporting of echocardiographic data at pre-defined follow-up intervals, which make data interpretation problematic if these conditions are not observed.[10]

Assessment and quantification of bioprosthetic valve dysfunction

The clinical course of patients with bioprosthetic valves should be monitored periodically, with the interval between routine follow-up visits determined according to cardiac status, comorbidities, and other clinical factors. Various imaging techniques are available for detection of bioprosthetic valve dysfunction. These include 2D/3D echocardiography, multi-detector computed tomography (MDCT) and magnetic resonance imaging (MRI).[11–13] Echocardiography is a 'functional' imaging modality and superior for the demonstration of valve haemodynamics (i.e. increased transvalvular gradient, valve regurgitation), whereas MDCT provides more 'anatomical' and structural information. MRI has the potential to combine anatomical and functional information but is not always readily available and experience in the assessment of bioprosthetic valve dysfunction is limited. These considerations have implications for the application of different imaging modalities in the assessment of bioprosthetic valve durability.

Echocardiography

Periodic echocardiographic surveillance is currently the reference standard for detection of SVD in cases unidentified at reoperation or autopsy. Stenosis or regurgitation of the bioprosthetic valve should be reported using validated quantitative or semi-quantitative methods.[9] The term deterioration implies changes intrinsic to the valve (including wear, fracture, calcification, leaflet tear, and/or disruption of any component). Transoesophageal imaging can improve visualization of morphological aspects of the valve prosthesis and the additional role of 3D echocardiography in this setting is yet to be defined.

Multi-detector computed tomography

Multi-detector computed tomography may be more sensitive than echocardiography in detecting valve thrombosis, particularly at early stages of the process (i.e. subclinical leaflet thrombosis without haemodynamic consequences).[14,15] Multi-detector computed tomography criteria for TAVI thrombosis include hypo-attenuated leaflet thickening (with or without reduced leaflet motion of one or more leaflets, identifiable in two or more multiplanar curved reconstructions).[11] Specific MDCT measurements include stent frame expansion and eccentricity index, number of leaflets with hypo-attenuated leaflet thickening, as well as degree of leaflet thickening, motion reduction and calcification.[11] Importantly, MDCT cannot determine aortic valve gradients and is therefore of diminished utility for the diagnosis of SVD.

Table 1 Long-term durability after surgical aortic valve replacement

Author	Year	N	Prosthesis	Results
David et al.[16]	2010	1134	Hancock II	• Survival: 19 ± 2% and 7 ± 3% at 20 and 25 years, respectively • Freedom from SVD[a]: 63 ± 4% at 20 years • Freedom from reoperation: 65 ± 4% at 20 years
Mohammadi et al.[17]	2012	430	Freestyle	• Survival: 60.7% and 35.0% at 10 and 15 years, respectively • Freedom from reoperation: 91.0% and 75.0% at 10 and 15 years, respectively • Freedom from reoperation for SVD[b]: 95.9% and 82.3% at 10 and 15 years, respectively
Forcillo et al.[18]	2013	2405	Carpentier-Edwards	• Survival: 78 ± 2%, 55 ± 2%, 34 ± 2%, and 16 ± 2% at 5, 10, 15, and 20 years, respectively • Freedom from reoperation: 98 ± 0.2%, 96 ± 1%, and 67 ± 4% at 5, 10, and 20 years, respectively
Senage et al.[19]	2014	617	Mitroflow	• Survival: 70% at 20 years • Freedom from SVD[c]: 92% at 5 years
Bourguignon et al.[10]	2015	2758	Carpentier-Edwards	• Survival: 14 ± 2% at 20 years • Valve-related survival: 64 ± 4% at 20 years • Freedom from SVD[d]: 79 ± 2% and 49 ± 5% at 15 and 20 years, respectively • Freedom from explant due to SVD[d]: 84 ± 2% and 54 ± 5% at 15 and 20 years, respectively
Johnstone et al.[5]	2015	12 569	Carpentier-Edwards	• Incidence of explant due to SVD[a]: 2% and 15% at 10 and 20 years, respectively

SVD, structural valve deterioration.
[a]Undefined.
[b]Defined as any change in function resulting from any valve abnormality excluding infection or thrombosis.
[c]Defined as progression of aortic transprosthetic gradient $\geq$30 mmHg associated with a decreased effective orifice area $\leq$1 cm^2 or intra-prosthetic aortic regurgitation >2/4.
[d]Defined as severe aortic stenosis (mean transvalvular gradient >40 mmHg) or severe aortic regurgitation (effective regurgitant orifice area >0.30 cm^2, vena contracta >0.6 cm).

Long-term outcomes of bioprosthetic valves in the aortic position

Surgical bioprostheses

Several large series have reported the long-term outcomes of SAVR bioprostheses with mixed results (*Table 1*). Importantly, the age of patients undergoing SAVR in these studies was on average lower than that of patients included in TAVI series, which makes cross-study comparisons inappropriate on the ground of long-term durability. As noted above, some of the surgical series evaluate durability in terms of survival or survival without reintervention; others expand the definition of SVD with criteria of haemodynamic progression. In a large series evaluating 2405 Carpentier-Edwards bioprostheses, survival without reintervention was 98 ± 0.2%, 96 ± 1%, and 67 ± 4% at 5, 10, and 20 years, respectively.[18] Bourguignon et al.[10] evaluated 2758 Carpentier-Edwards bioprostheses using clinical and echocardiographic criteria, and reported SVD in 157 patients (123 of whom required reintervention) over a cumulative follow-up of 18 404 valve-years. All cases of SVD were late events and actuarial freedom from SVD at 15 and 20 years was 78.6 ± 2.2% and 48.5 ± 4.6%, respectively. In the Johnstone et al.[5] series assessing SVD in 12 569 patients (81 706 patient-years), actuarial estimates of explant for SVD at 10 and 20 years were 1.9% and 15% overall. Porcine bioprostheses (Hancock II) have also demonstrated long-term durability in patients aged 60 years or older[16] while an accelerated pattern of SVD was observed with the Mitroflow prosthesis in approximately one-third of patients.[19] A study of 430 patients treated with a stentless bioprosthesis reported freedom from reoperation in 91.0% and 75.0% at 10 and 15 years, and freedom from reoperation for SVD in 95.9% and 82.3%, respectively.[17] Notably, outcomes vary with different surgical bioprostheses as demonstrated in recent post-market surveillance of 43 782 valves in England and Wales.[20]

Transcatheter bioprostheses

Transcatheter aortic valve implantation has only been widely available since 2007 and mainly used in elderly patients, in whom data concerning long-term durability are limited (*Table 2*). Serial annual echocardiography in the PARTNER A trial comparing TAVI using a balloon-expandable prosthesis with SAVR in high-risk subjects[22] demonstrated unchanged transvalvular gradient and aortic valve area up to 5 years (although only 53 patients remained at risk at 5-year follow-up). Published follow-up data of a pivotal trial using a self-expanding TAVI prosthesis vs. SAVR are available up to 3 years, suggesting more favourable valve haemodynamics for TAVI without differences in SVD.[24] In this trial, severe patient-prosthesis mismatch was more common in patients treated with SAVR than those treated with TAVI, and associated with higher 1-year mortality.[25]

The Canadian and Italian Registries demonstrated stable valve gradients over 5 years and very low rates of SVD of 3.4% and 4.2%, respectively.[21,23] However, it should be noted that few patients were still alive at 5 years (reflecting their advanced age and significant comorbidities at the time of valve implantation) and that definitions of SVD were not comparable. Only two unpublished single-centre series currently provide data on 'long-term' durability (>5 years) in patients treated before 2011 (Eltchaninoff et al.[26] Webb et al.[27] both presented at Transcatheter Valve

Table 2 Long-term durability after transcatheter aortic valve implantation

Author	Year	N	Prosthesis	Results
Toggweiler et al.[21]	2013	88	Cribier-Edwards or Edwards Sapien	• Survival: 35% at 5 years
Mack et al.[22]	2015	348	Edwards Sapien	• Mortality: 68% at 5 years
				• Reintervention due to SVD[a]: 0% at 5 years
Barbanti et al.[23]	2015	353	Medtronic CoreValve	• Mortality: 55% at 5 years
				• Bioprosthetic valve dysfunction: 1.4% at 5 years

SVD, structural valve deterioration.
[a]Undefined.

Therapeutics, Chicago, 2016). In the Rouen series ($n = 242$), SVD was defined as mean transvalvular gradient $\geq$20 mmHg plus an increase >10 mmHg over time and/or $\geq$moderate aortic regurgitation that was not present 30 days following valve implantation. Using this definition, only 1 patient had 'definite' SVD (redo TAVI for elevated gradient) and 3 asymptomatic patients had 'possible' SVD (mean gradient >20 mmHg and increase >10 mmHg in comparison with 30-day echocardiography). No patients had a gradient >40 mmHg. In the Vancouver series ($n = 266$), freedom from SVD defined as need for reintervention was 97.6% while freedom from SVD defined as severe stenosis, regurgitation or need for reintervention was 84.6% (both at 8-year follow-up). Overall, three patients were alive >10 years after TAVI with no signs of SVD (one in France, two in Canada).

Suggested definitions of structural valve deterioration and bioprosthetic valve failure

In building standardized definitions for the purpose of future studies, the Task Force reached consensus on the following points:

(1) There should be clear distinction between SVD (the principal aetiology) and BVF (the clinical correlate).
(2) Structural valve deterioration causes irreversible dysfunction whereas other pathological causes of bioprosthetic valve dysfunction (i.e. thrombosis, endocarditis) are potentially reversible and should be identified and categorized separately. However, the thrombotic or endocarditic process qualifies as a cause of BVF if it leads to lasting or permanent bioprosthetic valve dysfunction.
(3) Non-structural valve dysfunction (i.e. intra-prosthetic or paravalvular regurgitation, prosthesis malposition, patient-prosthesis mismatch, late embolization) may occur early after TAVI as a result of technical issues. Non-structural valve dysfunction resulting in valve-related death, reintervention, and haemodynamic dysfunction [i.e. severe new or worsening (>2+/4+) paravalvular aortic regurgitation] qualifies as a cause of BVF.
(4) Echocardiography is the principal imaging modality for the detection of SVD and the best and most accessible way to detect serial changes in valve function. Transprosthetic gradients should be determined in at least two consecutive measurements to account for detection bias and minimize inconsistencies related to the different types of bioprosthesis implanted. After TAVI and SAVR,

echocardiography should be performed before discharge or within 30 days after valve implantation (i.e. baseline imaging), at 1 year after valve implantation and annually thereafter (with additional follow-up assessments and/or integration of other imaging modalities as necessary and/or determined by the attending physician) (*Figure 2*).

Structural valve deterioration

Structural valve deterioration includes permanent intrinsic changes of the valve (i.e. leaflet tear, calcification, pannus deposition, flail, or fibrotic leaflet) leading to degeneration and/or dysfunction, which in turn may result in stenosis or intra-prosthetic regurgitation (*Table 3*). Structural valve deterioration can be detected using imaging studies or at the time of reoperation or autopsy, and can arise in both symptomatic and asymptomatic patients. Structural valve deterioration can be characterized as 'haemodynamic dysfunction' and/or 'morphological SVD'.
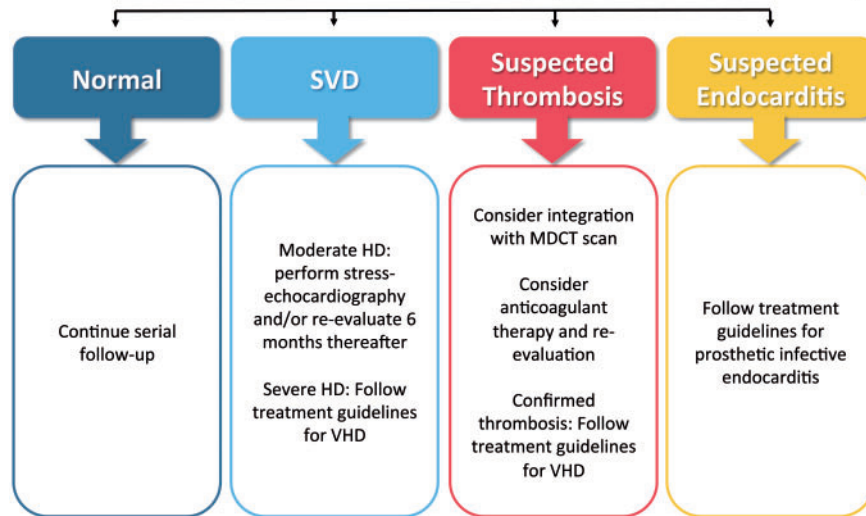
Haemodynamic structural valve deterioration

The diagnosis is based on permanent haemodynamic changes in valve function assessed by means of echocardiography, even without evidence of morphological SVD ('isolated haemodynamic dysfunction'). Morphological SVD may be diagnosed in patients with haemodynamic SVD by echocardiography or other imaging modalities. For simplicity, the Task Force specifies two degrees of haemodynamic SVD (moderate and severe—the detection of mild haemodynamic dysfunction being of less clinical importance). Moderate SVD is defined as (i) mean gradient $\geq$20 and <40 mmHg and/or $\geq$10 and <20 mmHg change from baseline (before discharge or within 30 days of valve implantation) and/or (ii) moderate new or worsening (>1+/4+) intra-prosthetic aortic regurgitation. Severe haemodynamic SVD is defined as (i) mean gradient $\geq$40 mmHg and/or $\geq$20 mmHg change from baseline (before discharge or within 30 days of valve implantation) and/or (ii) severe new or worsening (>2+/4+) intra-prosthetic aortic regurgitation.

Morphological structural valve deterioration

The diagnosis is based on imaging findings, regardless of whether reintervention is performed. In case of autopsy, the diagnosis of morphological SVD should be reassessed and confirmed or rejected based on the pathological findings. Morphological SVD encompasses abnormalities of the following domains: leaflet integrity (i.e. torn or flail causing intra-frame regurgitation), leaflet structure (i.e.

Figure 2 Suggested management algorithm at echocardiographic follow-up. HD, haemodynamic dysfunction; MDCT, multi-detector computed tomography; SVD, structural valve deterioration; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; VHD, valvular heart disease.

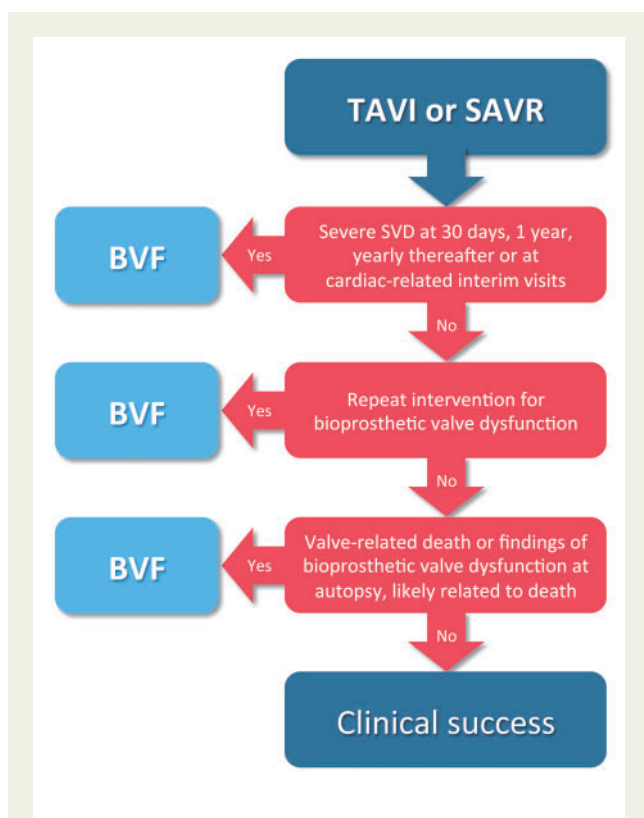| Table 3   Structural valve deterioration |
|---|
| Moderate haemodynamic SVD (any of the following) |
| Mean transprosthetic gradient ≥20 mmHg and <40 mmHg |
| Mean transprosthetic gradient ≥10 and <20 mmHg change from baseline |
| Moderate intra-prosthetic aortic regurgitation, new or worsening (>1+/4+) from baseline |
| Severe haemodynamic SVD (any of the following) |
| Mean transprosthetic gradient ≥40 mmHg |
| Mean transprosthetic gradient ≥20 mmHg change from baseline |
| Severe intra-prosthetic aortic regurgitation, new or worsening (>2+/4+) from baseline |
| Morphological SVD (any of the following) |
| Leaflet integrity abnormality (i.e. torn or flail causing intra-frame regurgitation) |
| Leaflet structure abnormality (i.e. pathological thickening and/or calcification causing valvular stenosis or central regurgitation) |
| Leaflet function abnormality (i.e. impaired mobility resulting in stenosis and/or central regurgitation) |
| Strut/frame abnormality (i.e. fracture) |
| Haemodynamic and morphological SVD |

SVD, structural valve deterioration.

pathological thickening and/or calcification causing valvular stenosis or central regurgitation), leaflet function (i.e. impaired mobility resulting in stenosis and/or central regurgitation), and strut/frame (i.e. fracture or failure).

Bioprosthetic valve failure

The term BVF integrates severe SVD (i.e. the aetiology) with its clinical consequences (thereby avoiding over-interpretation of valve-related outcomes in asymptomatic patients with no clinical impact) and is recommended by the Task Force as the main outcome of interest in studies assessing the long-term performance of TAVI and SAVR (*Figure 3*, *Table 4*). Importantly, BVF may occur in the setting of SVD but also as the consequence of pathophysiological processes unrelated to SVD, such as thrombosis, endocarditis or non-structural valve dysfunction. BVF includes any of the following: (i) bioprosthetic valve dysfunction at autopsy, very likely related to the cause of death, or 'valve-related death', defined as any death caused by bioprosthetic valve dysfunction in the absence of confirmatory autopsy; (ii) aortic valve reintervention (i.e. valve-in-valve TAVI, paravalvular leak closure or SAVR); and (iii) severe haemodynamic SVD. Based on the degree of certainty, BVF can be categorized as definite (i.e. autopsy, reintervention, severe haemodynamic SVD) or probable (i.e. valve-related death), and early (i.e. up to 30 days) or late (i.e. >30 days) according to the timing of onset after valve implantation.

Survival analysis for bioprosthetic valve failure: key considerations

Assessing the durability of biological prostheses poses important challenges and a number of preliminary questions. First, should BVF be considered a longitudinal or time-dependent outcome measure? Second, what is the inherent bias of estimating BVF in an elderly population? Third, is there a statistical approach to best address these

Figure 3 Suggested assessment of bioprosthetic valve failure (BVF) in outcome studies of transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR). SVD, structural valve deterioration.

Table 4 Bioprosthetic valve failure

Autopsy findings of bioprosthetic valve dysfunction, likely related to the cause of death, or valve-related death (i.e. any death caused by bioprosthetic valve dysfunction or sudden unexplained death following diagnosis of bioprosthetic valve dysfunction)

Repeat intervention (i.e. valve-in-valve TAVI, paravalvular leak closure or SAVR) following confirmed diagnosis of bioprosthetic valve dysfunction

Severe haemodynamic SVD

SAVR, surgical aortic valve replacement; SVD, structural valve deterioration; TAVI, transcatheter aortic valve implantation.

challenges? The following paragraphs will discuss these points and focus on best practice in survival analysis for BVF.

Longitudinal vs. time-dependent outcomes

An important preliminary distinction is between valve and patient outcomes. Valve outcomes pertain to the intrinsic durability of the bioprosthesis (i.e. they address the question 'what is the probability of this valve lasting over time without failure?'). In contrast, patients are more interested in their individual probability of experiencing a valve failure-related event during their remaining lifetime (i.e. 'what is the probability of my valve failing before I die?'). Importantly, some valve outcomes (including haemodynamic SVD) are typically longitudinal in nature, which means that they evolve with time and do not occur at a precise instant. To capture valve outcomes while minimizing bias, it is important to consider the timing of observations, or 'snapshots'. For example, when assessing the presence or absence of haemodynamic SVD by measurement of mean gradient using Doppler echocardiography, there is an important difference if the snapshots are infrequent while the observed condition changes rapidly (which introduces data aliasing). On the other hand, there is a risk of overestimating adverse valve outcomes if the snapshots are opportunistic (i.e. if echocardiography is performed at any time in symptomatic patients). These issues are obviously magnified when snapshots are heterogeneously derived across different patient cohorts. At variance with valve outcomes, patient outcomes are more typically time dependent in that they reflect the occurrence of an event from the time of implantation to a precise landmark (i.e. death or reintervention).

Competing risk and informative censoring

Death exerts a competing risk against the risk of a valve to fail over time. In fact, if the patient dies at a time when the valve is functioning normally, then there is no way to predict how long the valve would have lasted if the patient had survived. In other words, if BVF occurs at some time during follow-up, then the end point is easily captured. In contrast, if the patient dies with no bioprosthetic valve dysfunction, we cannot be sure about the true durability of the prosthesis because death obscures the chance for that valve to become dysfunctional at a later time point. This bias is obviously more likely to occur in an old and frail population (where the mortality rate is higher *per se*). The term 'censoring' refers to the situation when the information regarding an end point for a given patient is only partially known. For example, a patient may be censored in a study of TAVI durability because (i) BVF does not occur during the follow-up period; (ii) the patient dies before the end of the follow-up period (i.e. competing risk); or (iii) the patient is lost to follow-up. A typical assumption of outcome studies is that censoring can be ignored or is non-informative. Based on such an assumption, the survival experience of a patient who dies or is lost to follow-up may be completed by statistical means (i.e. Kaplan–Meier analysis) and the outcome of interest estimated as part of a virtual 'death-free environment' where all patients reach final follow-up assessment. However, the typical assumption of non-informative censoring is false in TAVI durability studies. Indeed, there is a clear dependence between the competing risk of death and BVF (i.e. informative censoring) in that (i) patients who die before BVF are generally older than those who do not and (ii) the rate of BVF is lower in older patients.

Actuarial vs. actual analysis

The relevant question for a TAVI patient does not necessarily pertain to the intrinsic durability of the valve, but to the probability of a clinical event related to bioprosthetic valve dysfunction during the course of the remaining life. In this regard, conventional Kaplan–Meier analysis (a type of actuarial analysis) may lead to incorrect
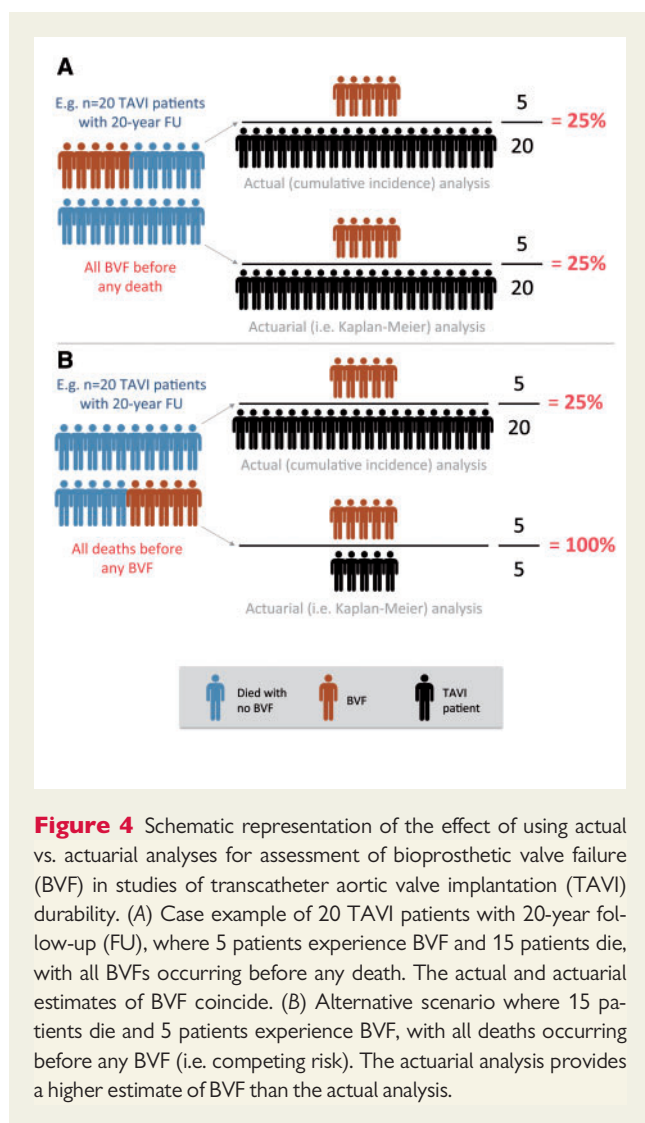
Figure 4 Schematic representation of the effect of using actual vs. actuarial analyses for assessment of bioprosthetic valve failure (BVF) in studies of transcatheter aortic valve implantation (TAVI) durability. (*A*) Case example of 20 TAVI patients with 20-year follow-up (FU), where 5 patients experience BVF and 15 patients die, with all BVFs occurring before any death. The actual and actuarial estimates of BVF coincide. (*B*) Alternative scenario where 15 patients die and 5 patients experience BVF, with all deaths occurring before any BVF (i.e. competing risk). The actuarial analysis provides a higher estimate of BVF than the actual analysis.

estimates, since each event causes an increasingly significant drop of the curve for survival free from BVF (as long as censoring occurs over the duration of follow-up) (*Figure 4*). Kaplan–Meier estimates may be useful for those interested in the hypothetical durability of a valve 'assuming patients' immortality', particularly if statistical correction for informative censoring is applied. Indeed, the statistical method of inverse probability weighting may correct for the bias of informative censoring and provide a better estimate of true valve performance. Importantly, specific rules for the correct reporting of Kaplan–Meier curves should be respected: (i) indicating the number of patients at risk at each time point below the x-axis; (ii) reporting 95% confidence intervals; and (iii) cutting the event-free survival curve when less than 10% of the initial patient cohort is available. In contrast to the actuarial method, the actual method is the correct probability that should be used for clinical predictions, patient management decisions and cost-effectiveness studies. This method, based on a cumulative incidence function, provides lower estimates than actuarial Kaplan–Meier analysis and might have greater clinical utility in the context of TAVI durability studies.

Areas of future research and implications for study design

The dawn of a new era in the treatment of valve disease using transcatheter techniques is ongoing. The clinical successes of TAVI are increasingly well described by both randomized trials and observational research. However, in the process of moving to less invasive treatment of younger and lower risk patients, it is important to better appraise the long-term durability characteristics of current and future TAVI prostheses. To better achieve this goal, we have proposed practical and standardized definitions of SVD and BVF and provide recommendations for the timing and modalities of clinical and imaging follow-up assessment. For the sake of comparability, these should also be extended to the evaluation of current and future surgical bioprostheses, whose long-term efficacy and durability are currently addressed by a surprisingly small body of literature.

Important information concerning bioprosthetic valve dysfunction and BVF, and their relationship with individual patient characteristics, bioprosthetic valve design and techniques for valve implantation will provide valuable data to guide new developments in technology and implantation techniques. Accepted and carefully defined imaging characteristics will allow identification of bioprosthetic valve dysfunction due to mechanical factors, endocarditis and thrombotic phenomena. While the degenerative process seems comparable in frequency and anatomical/pathological characteristics to that observed with surgical bioprostheses,[28,29] recent evidence of valve leaflet thickening and thrombosis requires further investigation since (i) it remains unclear whether these phenomena are of clinical relevance and somehow linked to SVD[12] and (ii) the optimal antithrombotic regimen for this condition is yet to be determined.

Within the EORP programme, EAPCI aims to coordinate a large European registry of TAVI patients treated >5 years ago by engaging the pioneering European centres who started TAVI programmes at the early inception of this treatment strategy. The registry will focus on two main aspects of data collection: (i) prevalence of BVF at latest follow-up and (ii) progression of SVD in patients treated at different time intervals. Some important remaining gaps in knowledge that need to be recognized include the minimal follow-up data beyond 10 years and our inability to address the significant changes in device characteristics and procedural techniques over time.[30] Notwithstanding these limitations, the results of the EAPCI/EORP registry will be instrumental in achieving a better understanding of current results and the opportunities for TAVI in younger patients. Moreover, they will provide a benchmark for comparing the results of TAVI with those of surgically implanted valves.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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