Biomarkers of aortic bioprosthetic valve structural degeneration

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Purpose of review
Bioprosthetic valves are now used for the majority of surgical aortic valve replacements and for all transcatheter aortic valve replacements. However, bioprostheses are subject to structural valve deterioration (SVD) and have, therefore limited durability.

Recent findings
Clinical, imaging, and circulating biomarkers may help to predict or indicate the presence of bioprosthetic valve SVD. The most important biomarkers of SVD includes: patient-related clinical biomarkers, such as diabetes and renal failure; valve-related biomarkers, such as absence of antimineralization process and severe prosthesis-patient mismatch; imaging biomarkers: the presence of valve leaflet mineralization on multidetector computed tomography or sodium fluoride uptake on positron emission tomography; and circulating biomarkers including: increased levels of HOMA index, ApoB/ApoA-I ratio, PCSK9, Lp-PLA2, phosphocalcic product. The assessment of these biomarkers may help to enhance risk stratification for SVD following AVR and may contribute to open novel pharmacotherapeutic avenues for the prevention of SVD.

Summary
SVD may affect all bioprostheses after aortic valve replacement, and is the main cause of bioprosthetic valve failure and reintervention during the follow-up. Comprehensive assessment of clinical, imaging, and circulating biomarkers associated with earlier SVD could help strengthen the follow-up in high-risk patients and provide novel pharmacologic therapeutic strategies.

Keywords
biomarkers, hemodynamic and structural structural valve deterioration, inflammation, lipids, multidetector computed tomography, patient–prosthesis mismatch, phosphocalcic metabolism

INTRODUCTION

The incidence and prevalence of heart valve diseases are increasing exponentially worldwide with the aging of the population, and now afflict more than 100 million people [1,2]. Aortic stenosis, is the most common valve disease [3,4]. Implantation of prosthetic valves remain the only available option for the treatment of severe aortic valve disease. Aortic valve replacement (AVR) is, indeed, indicated when aortic stenosis is severe, symptomatic and/or left ventricle systolic dysfunction is present [5,6]. The ratio of bioprosthetic versus mechanical valves implanted during surgical AVR (SAVR) increased markedly during the past decade [7]. The age limit recommended to consider implantation of a bioprosthetic rather than a mechanical valve for SAVR is at least 50 years in the 2017 update of American Heart Association–American College of Cardiology (AHA–ACC) guidelines and at least 60 years in the 2017 European Society of Cardiology–European Association for Cardio-Thoracic Surgery (ESC-EACTS) guidelines [6,8]. Moreover, younger patients or those with an active lifestyle frequently choose a bioprosthetic valve to avoid life-long anticoagulant therapy required after mechanical valve implantation. Bioprosthetic valves are however, subject to structural valve deterioration (SVD), and therefore have limited durability with at least 30% of valves presenting signs of structural and hemodynamic deterioration at 10 years post AVR [9,10▪▪,11].

In parallel to this increase in the use of surgical aortic bioprostheses, transcatheter AVR (TAVR) using transcatheter bioprosthetic valves has emerged and expanded rapidly as: the treatment of choice for elderly patients with symptomatic severe aortic

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KEY POINTS

- Bioprosthetic valves are used for the majority of surgical aortic valve replacements and for all transcatheter aortic valve replacements, but bioprosthetic valves are subject to SVD.
- The most important biomarkers of SVD includes: patient-related biomarkers; valve-related biomarkers.
- Increased levels of HOMA index, ApoB/ApoA-I ratio, PCSK9, Lp-PLA2, and phosphocalcic product are the main circulating biomarkers associated with SVD.
- The assessment of biomarkers may help to enhance risk stratification for SVD following AVR and may contribute to open novel pharmacotherapeutic avenues for the prevention of SVD.

stenosis who are at high or extreme risk for surgery; [6,8] a reasonable alternative to SAVR in patients with intermediate surgical risk; [6,8] a possible future alternative to SAVR in patients with low surgical risk [12]. Despite excellent short-term and mid-term clinical outcomes observed in patients undergoing TAVR, several studies reported cases of valve thrombosis or SVD [13]. Bioprosthetic valve dysfunction related to thrombosis or SVD is a complex involving several patient-related and prosthesis-related related factors [14▪,15,16▪].

The purpose of this review is to provide an overview of SVD definition and to present clinical, imaging and circulating biomarkers of bioprosthetic SVD.

DEFINITION OF STRUCTURAL VALVE DETERIORATION

SVD is a gradual process characterized by fibrocalcic remodeling, thickening and stiffening of valve leaflets and/or disruption of collagen fibers ensuing leaflet tear or perforation [17]. This intrinsic tissue deterioration often leads to bioprosthetic valve hemodynamic dysfunction, that is stenosis (~ 40% of cases), regurgitation (~ 30%) or combined stenosis and regurgitation (~ 30%) [10▪▪]. To date, there is no unified consensus regarding the definition of SVD. In most SAVR series, SVD was defined merely on the basis of reoperation for hemodynamic valve failure [18,19]. This approach based on reintervention may substantially underestimate the true incidence of SVD. Indeed, an important proportion of patients with significant SVD ultimately do not undergo reoperation because: their SVD is underdiagnosed or underestimated; they are not currently at the stage of SVD requiring reintervention; or they are considered at too high risk for reoperation [16▪].

More recent studies have rather utilized a definition of SVD based on echocardiographic assessment of the bioprosthetic valve morphology and function during follow-up [20–22].

Two recent consensus statements (European Association of Percutaneous Cardiovascular Interventions-EACPI, and Valve in Valve International Data-VIVID) [23▪▪,24▪▪] and one recommendation (European Association of Cardiovascular Imaging-EACVI) [10▪▪] proposed definitions of SVD based on the new onset or worsening of morphological and functional abnormalities of the bioprostheses by Doppler echocardiography and/or multidetector computed tomography (MDCT). The four-stage classification presented below [14▪] (Table 1) represents the compendium of the different classifications proposed by these three documents:

(1) Stage 0 – no SVD: normal valve morphology and function. An annual clinical and echocardiographic follow-up should be considered in these patients.
(2) Stage 1 – morphological SVD: morphological abnormalities of valve leaflets characterized by calcification, fibrosis, thickening, and stiffening assessed by echocardiography and/or noncontrast MDCT. These irreversible abnormalities compromise the structural integrity of the leaflets. At stage 1, there is no evidence of hemodynamic deterioration of the valve and thus no impact on the patient's symptomatic status, left ventricular (LV) function or pulmonary arterial pressure. In Stage 1 SVD, a trial of anticoagulation should be considered if subclinical leaflet thrombosis is suspected.
(3) Stage 2 – moderate hemodynamic SVD: more advanced bioprosthetic valve tissue degeneration associated with the presence of moderate hemodynamic valve deterioration (HVD). Stage 2 SVD may lead to onset or worsening of symptoms, LV dysfunction and/or pulmonary hypertension in more vulnerable patients. Of note, patients with Stage 1 or 2 SVD should receive close clinical and Doppler echocardiography follow-up every 3–6 months. Re-intervention may be considered in patients with Stage 2 SVD if the patients is symptomatic and the symptoms are believed to be related to SVD.
(4) Stage 3 – severe hemodynamic SVD: advanced morphological tissue degeneration associated with severe HVD. This stage is often associated with onset or worsening of symptoms, LV dilatation/hypertrophy/dysfunction and/or pulmonary hypertension. Patients with Stage 3 SVD generally require valve re-intervention.

Table 1. Definition of structural valve deterioration of aortic bioprostheses

	Stage 0[d] No SVD	Stage 1[d] SVD with no HVD 'Morphological SVD'[c]	Stage 2[d] SVD with moderate HVD 'Moderate Haemodynamic SVD'[c]	Stage 3[d] SVD with severe HVD 'Severe haemodynamic SVD'[c]
Valve leaflet morphology and motion by TTE, TEE, or MDCT				
Leaflet morphology				
Valve leaflet thickening:	Absent	Present	Present	Present
At least one leaflet with thickness $\geq$ 2 mm				
Valve leaflet fibro-calcific remodeling:	Absent	Present	Present	Present
Hyper-echogenicity (TTE/TEE) or hyper-density (MDCT)				
Detectable leaflet calcification at MDCT				
Leaflet motion				
Reduced mobility	Absent	Absent or mild	Mild to Moderate	Moderate to Severe
Leaflet tear/avulsion	Absent	Absent	May be present	May be present
Valve haemodynamics by TTE				
Mean transprosthetic gradient				
Absolute increase from baseline[b]	< 10 mmHg	< 10 mmHg	10–19 mmHg	$\geq$ 20 mmHg
Mean gradient at post-AVR echo[a]	< 20 mmHg	< 20 mmHg	20–39 mmHg	$\geq$ 40 mmHg
Valve effective orifice area				
Absolute decrease from baseline	<0.30 cm^2	<0.30 cm^2	0.30–0.59 cm^2	$\geq$ 0.60 cm^2
Doppler velocity index				
Absolute decrease from baseline	<0.1	<0.1	0.1–0.2	$\geq$ 0.2
Central prosthetic valve regurgitation[b]				
Worsening compared with baseline	Absent	None	$\geq$1 Grade	$\geq$2 Grades
Grade of regurgitation	None, Trace, or Mild	None, Trace, or Mild	Moderate	Severe

Clinical status	**Subclinical**	**Often subclinical**	**Generally clinically expressive**
New onset or worsening symptoms	Absent	Often absent	Generally present
New onset or worsening LV dilation/hypertrophy/dysfunction	Absent	Generally absent	Often present
New onset or worsening pulmonary hypertension	Absent	Generally absent	Often present

The classification and criteria presented are based on recommendations and standardized definitions of medical societies or group of experts [10▪▪,23▪▪,24▪▪]. Stage 0 refers to a normal valve. Stage 1 consists in the presence of morphological abnormalities of valve leaflets but with no evidence of HVD. At echocardiography, the leaflets are thickened (>2 mm), often irregular, and hyperechogenic. MDCT without contrast may be used to detect and quantitate macroscopic valve leaflet calcification by the modified Agatston method or the volumetric method. Stage 2 consists in SVD with moderate HVD defined as: an increase in mean transprosthetic gradient at least 10 mmHg since early post-SAVR or TAVI echocardiography with concomitant decrease in valve effective orifice area (EOA) and Doppler velocity index (DVI); and/or a new onset or worsening of central prosthetic regurgitation by at least one grade with a final grade of moderate. An increase in transprosthetic velocity and gradients with concomitant increase in valve EOA and DVI is actually related to an increase in flow during follow-up and should not be mistaken for a HVD. Stage 3 consists in SVD with severe HVD characterized by: an increase in mean transprosthetic gradient at least 20 mmHg since SAVR or TAVI with concomitant marked decrease in valve EOA and DVI and/or new onset or worsening of transprosthetic regurgitation by at least two grades with final grade of severe regurgitation. Adapted with permission from Salaun *et al.* [14▪]. AVR, aortic valve replacement; HVD, haemodynamic valve deterioration; SVD, structural valve deterioration; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]This criteria is corroborative but should not be used in isolation to define haemodynamic SVD.

[b]The most important criteria to define haemodynamic HVD is a significant increase in mean transprosthetic gradient with concomitant decrease in valve-effective orifice area and Doppler velocity index; and/or a new onset or a worsening of central prosthetic valve regurgitation.

[c]Classification terminology proposed by Capodanno *et al.* [23▪▪].

[d]Classification terminology proposed by: Dvir *et al.* [24▪▪].

BIOMARKERS

Biomarkers can be diagnostic, surrogate, prognostic, or predictive of a condition or a disease. They offer an accessible way to gather and deepen the information that may refine or clarify patient''s risk profile and help for therapeutic decision-making. Although Doppler echocardiography is presently the gold standard for the diagnosis of SVD, a number of clinical, imaging, and circulating biomarkers have been proposed for the noninvasive assessment of this complication (Fig. 1).

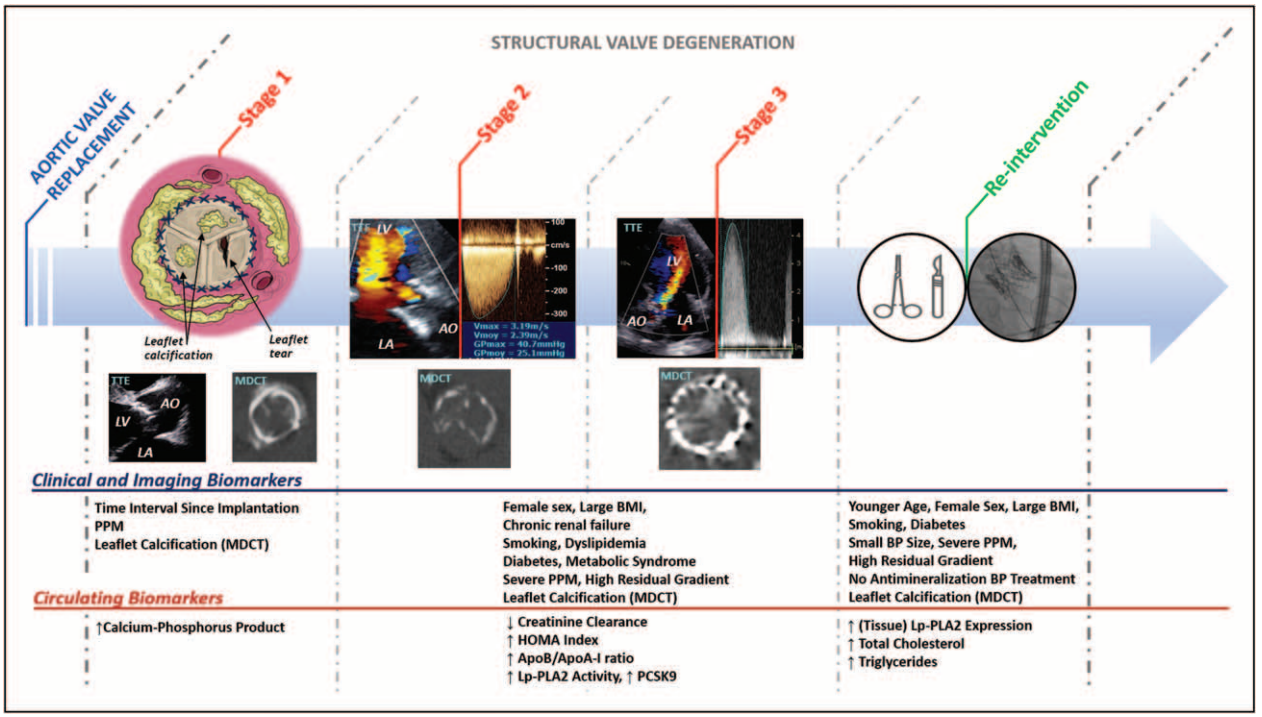

FIGURE 1. Clinical, imaging, and circulating biomarkers of structural valve deterioration of aortic bioprosthetic valves. AO, aorta; BP: bioprosthetic valve; LA, left atrium; LV, left ventricle; MDCT, multidetector computed tomography; PPM, prosthesis–patient mismatch; TTE, transthoracic echocardiography.

CLINICAL AND IMAGING BIOMARKERS OF STRUCTURAL VALVE DETERIORATION

Clinical and imaging biomarkers can be divided into two main categories: patient-related biomarkers and valve-related biomarkers (Fig. 1) [15].

Patient-related biomarkers

Among the factors related to the patient, younger age at the time of valve implantation has been one of the most important factors associated with reintervention for bioprosthetic valve failure [18,25–27]. However, this finding should not lead to the conclusion that younger age is a powerful predictor of accelerated SVD. Indeed, studies based on re-operation are flawed by the fact that, for the same degree of SVD, younger patients are much more likely to be reoperated than older patients. As a matter of fact, the majority of the studies that used a definition of SVD based on imaging criteria (rather than on reintervention) found no association between age and SVD [22]. Female sex was interestingly associated with both Stage 2 [16▪] and Stage 3 [21,28] SVD, and was a risk factor of reoperation for bioprosthetic valve failure [29]. This intriguing result may be linked to the calcification paradox, which associates altered bone mineralization metabolism in postmenopausal women with osteoporosis and ectopic calcification [30–32]. Ectopic calcification includes calcification of arterial walls but also of native and bioprosthetic valves [33,34]. Chronic renal failure is another factor associated with the progression of transprosthetic pressure gradient [35], and the occurrence of Stages 2 and 3 SVD [16▪,28]. Dysregulation of phosphocalcic metabolism and secondary hyperparathyroidism could also be involved in the pathogenesis of SVD [11,36]. Smoking is associated with earlier onset of Stage 2 SVD [16▪], and is also an independent risk factor of reoperation for SVD [27]. A potential explanation for this finding is that the increased oxidative stress associated with smoking may promote SVD by activating pro-fibrotic and pro-calcific mechanisms in the bioprosthetic aortic valve leaflets [37,38].

Larger BMI was associated with Stage 3 SVD [22], and reoperation for SVD [15]. This association may reflect the link between metabolic risk factors and SVD. Indeed, obesity is associated with diabetes, dyslipidemia, and metabolic syndrome, which have all previously been implicated in the degeneration of native and bioprosthetic valves [39].

Metabolic syndrome is a cluster of atherogenic, inflammatory, and atherothrombotic abnormalities, which is largely resulting from overweight/obesity and sedentary lifestyle [40]. This condition, which is considered a prediabetic stage, was found to associate with accelerated SVD following SAVR [35]. Metabolic syndrome is estimated to reach ≈25% in the western population [40], and negatively influences disease progression and prognosis

in native aortic stenosis [39]. One-third of patients implanted with aortic bioprostheses meet the definition of metabolic syndrome [35]. Type 2 diabetes is strongly associated with Stage 2 SVD [16▪], and with reoperation for bioprosthetic failure [29,41]. Furthermore, the risk of reoperation for SVD was higher in patients treated with insulin versus those treated with oral hypoglycemic agents [41]. Diabetes appears to be one of the most powerful determinant of SVD following AVR.

Valve-related biomarkers

Among the factors related to the valve, prosthesis–patient mismatch (PPM) [18], small bioprosthesis size [27,35], and high postoperative residual transprosthetic gradient [18] were associated with reintervention for bioprosthetic failure. The presence of PPM is predictor of SVD [11], and the risk of Stage 2 SVD increases with the severity of the PPM (hazard ratio 1.40 with no or mild PPM, hazard ratio 2.03 with moderate PPM, hazard ratio 2.84 with severe PPM) [16▪]. Moreover, severe PPM is also associated with increased risk of Stage 3 SVD [21].

The valve durability may vary depending on the type and design of bioprosthetic valve [16▪]. In particular, high rates of early valve failure were found in some specific models of bioprostheses. For example, the first generation of the Mitroflow valve exhibited higher risk of early SVD and valve failure [21,22]. The Toronto SPV bioprosthesis was found to have shorter durability compared with the other types of stentless bioprostheses [42].

A recent study suggests that surgical stentless bioprostheses are associated with lower risk of SVD and better survival compared with stented bioprostheses [16▪].

There is not yet any data on the long-term durability of transcatheter heart valves [14▪,43]. However, in patients with high or intermediate surgical risk, the comparison of the mid-term durability of TAVR versus SAVR are encouraging and there is no evidence that TAVR might be less durable than SAVR at least up to 7 years [44–46].

Emerging imaging biomarkers

Valve leaflet calcification is the main culprit lesion of SVD. The detection of leaflet calcification by noncontrast MDCT predicts the future development of Stage at least 2 SVD and the risk of death or valve reintervention in patients with surgical bioprosthetic valves [47]. Assessment of valve leaflet calcification by MDCT may also be useful to identify SVD of transcatheter bioprosthetic valves [13]. PET with sodium fluoride tracer is a very promising imaging tool for early detection of SVD in bioprosthetic valves [48].

Table 2. Circulating biomarkers and mechanisms implicated in aortic bioprosthetic valve degeneration

Mechanisms implicated in structural valve deterioration	Circulating biomarkers
Dysregulation of mineral metabolism	
	↑ Calcium-phosphorus product
	↓ Creatinine clearance
Lipid-mediated inflammation and metabolism processes	
	↑ HOMA index
	↑ Total cholesterol
	↑ Triglycerides
	↑ ApoB/ApoA-I ratio
	↑ PCSK9
	↑ Lp-PLA2
Immune inflammation and macrophage activation	
	↑ sCD14

HOMA, homeostatic model assessment; Lp-PLA2, lipoprotein-associated phospholipase A2; PCSK9, proprotein convertase subtilisin/kexin 9; sCD14, soluble CD14.

CIRCULATING BIOMARKERS

Several circulating biomarkers may provide additional information to predict the risk of developing SVD or mark the presence of SVD in patients with aortic bioprosthetic valves. Table 2 summarizes the mechanisms implicated in bioprosthetic valve SVD and the corresponding circulating biomarkers.

Biomarkers of phosphocalcic metabolism

Markers of dysregulation of mineral metabolism may be associated with increased risk of SVD. In particular, higher calcium–phosphorus product is strongly associated with bioprosthetic valve leaflet calcification (Stage 1 SVD) [11]. Renal failure often leads to increased circulating levels of calcium, phosphorus, and parathyroid hormones, which in turns promote ectopic calcification. Patients with preoperative creatinine clearance less than 30 ml/min have a two-fold increase in the risk of Stage at least 2 SVD within the first 5 years post-SAVR, compared with patients with clearance greater than 60 ml/min [16▪].

Lipid biomarkers

Other plasma biomarkers illustrate the implication of lipid-mediated inflammation in the development of SVD. The risk of reoperation for bioprosthetic valve failure is higher in patients with a total cholesterol at least 200 mg/dl or triglycerides levels at least 150 mg/dl [41], and in the subset of younger patients (<57 years) when total cholesterol was greater than 240 mg/dl or triglycerides level was

greater than 123 mg/dl [29]. These results support the hypothesis that the mechanisms involved in native as well as bioprosthetic aortic valve degeneration are different in younger versus older patients. In a cross-sectional study, patients with Stage 2 SVD had higher circulating levels of Apo-B and ApoB/ApoA-I ratio [49]. Homeostatic model assessment (HOMA) index calculated with the formula: insulin (μU/ml) $\times$ [glucose (mmol/l)/22.5), a marker of insulin resistance, was previously associated with faster hemodynamic progressions in patients with native aortic stenosis [50]. In a recent study, HOMA index has been associated with increased risk of SVD. The previously reported threshold to detect insulin-resistance (HOMA index $\geq$2.7) [51] was associated with higher risk of Stage 2 SVD [47].

The proprotein convertase subtilisin/kexin 9 (PCSK9) is primarily secreted from liver cells and binds to LDL receptor (LDLR) causing down regulation of the LDLR and leading to lysosomal destruction of LDLR. The overall effect of PCSK9 is to increase the circulating levels of LDL cholesterols [52]. In addition, PCSK9 is increased in patients with larger BMI, waist circumference, and insulin resistance. This biomarker is thus a cornerstone of the lipid metabolism, and promotes atherosclerosis at the systemic and tissue levels [53]. Moreover, high plasma level of PCSK9 ($\geq$305 ng/ml) and/or association of high levels of PCSK9 and oxidized-LDLs (PCSK9 $>$ 298 ng/ml and ratio oxidized-LDLs/HDL $\geq$25.4 U/l) are predictors of stage 2 HVD [47,54]. The effect of PCSK9 inhibitors on aortic stenosis are currently being investigated ('PCSK9 inhibitors in the progression of aortic stenosis,' Clinicaltrials.gov identifier: NCT03051360) and this therapy could be considered to prevent SVD following AVR.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is highly expressed in stenotic native aortic valves [55], and the plasma Lp-PLA2 activity is associated with faster progression of the native aortic valve disease [56]. Lp-PLA2 is an enzyme encoded by the *PLA2G7* gene and uses oxidized-LDLs as a substrate to produce free fatty acids and lysophosphatidylcholine promoting inflammatory activity. Among patients implanted with aortic bioprostheses, increased plasma levels of Lp-PLA2 activity is associated with the occurrence of SVD [47]. Moreover, about two-third of aortic bioprostheses explanted for SVD express Lp-PLA2, which also correlates with the density of macrophages (CD68), and oxidized-LDLs level in these tissues [57].

Inflammation biomarkers

Immune inflammation and macrophage activation are also suspected to participate in the development of SVD [9]. The implication of macrophages in SVD has been previously reported in explanted bioprostheses [58]. The macrophages were found in the areas of the leaflets where lipid deposits were present [59]. CD14 is a membrane glycoprotein expressed by monocytes and macrophages, and soluble CD14 (sCD14), resulting of the cleavage of membrane-bound CD14, may be assayed in the blood plasma. The liver also liberates sCD14 in circulation in response to inflammatory stimuli. In a recent work, circulating sCD14 was independently related to SVD of aortic bioprostheses [60].

CONCLUSION AND FUTURE PERSPECTIVES

Several clinical, imaging, and circulating biomarkers may help to predict or indicate the presence of SVD of aortic bioprosthetic valves. The most important biomarkers of SVD are: for patient-related clinical biomarkers: diabetes and renal failure; for the valve-related biomarkers: absence of antimineralization process and severe prosthesis–patient mismatch; for imaging biomarkers: the presence of valve leaflet mineralization on MDCT or sodium fluoride uptake on PET-CT; and for circulating biomarkers: increased levels of HOMA index, ApoB/ApoA-I ratio, PCSK9, Lp-PLA2, phospho-calcic product. Although further studies are needed to determine if these factors are only markers of SVD or factors that contribute to SVD, these findings may help to enhance risk stratification for SVD and may open novel pharmacotherapeutic avenues for the prevention of SVD. However, the ability of the circulating biomarkers that have been identified until now to mark or predict SVD remains limited. In the future, multiomic approach may help to identify the molecular signature of SVD, which would be particularly helpful to precisely predict the risk of SVD as well as to detect the presence of subclinical SVD.

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Conflicts of interest

P.P. received funding for echocardiography corelab analyses for studies on transcatheter and surgical bioprosthetic valves. All other authors have no conflicts of interest to disclose.

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