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REVIEW ARTICLE

Biomarkers in Aortic Stenosis: A Systematic Review

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ABSTRACT

Aortic stenosis (AS) is one of the most common heart valve diseases among adults. When symptoms develop alongside severe AS, there is a poor prognosis unless aortic valve replacement (AVR) is performed; however, many patients do not report symptoms even when AS is severe. The optimal timing of AVR for these patients remains uncertain and controversial. AS is a heterogeneous disease with a complex pathophysiology involving structural and biological changes of the valve as well as adaptive and maladaptive compensatory changes in the myocardium and vasculature in response to chronic pressure overload. Several biomarkers reflecting these processes have been identified and have shown to have utility in predicting symptom onset and clinical events before and after AVR. Herein we systematically review biomarkers that have been studied in the setting of AS and summarize their potential use for risk stratification and ultimately to guide the optimal timing of AVR.

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KEYWORDS Aortic stenosis; aortic valve; aortic valve replacement; asymptomatic; biomarkers

Introduction

Aortic stenosis (AS) affects approximatively 5% of the general population over the age of 65 years, and once symptoms develop it carries a dismal prognosis unless the valve is replaced.[1–18] Current guidelines, therefore, recommend surgical or transcatheter aortic valve replacement (AVR) for patients with severe symptomatic AS (class I).[19,20] Despite this fact, the optimal timing of intervention for patients with asymptomatic severe AS is uncertain and controversial.[5,21–29] Since mortality rates are low for isolated surgical AVR (SAVR) and transcatheter AVR (TAVR), earlier intervention has been increasingly advocated.[14,15,30–32] For asymptomatic patients, in particular, biomarkers may identify a subgroup of patients who would benefit from earlier valve replacement. Echocardiographic criteria of AS severity, based on anatomical and Doppler indices, have well-known limitations and can incorrectly classify as "moderate" AS patients with a more malignant AS phenotype who are at an increased risk of adverse events or rapid clinical AS progression.[33,34] Moreover, current criteria do not incorporate signs of maladaptive LV remodeling, such as severe LV hypertrophy or the presence of myocardial fibrosis, into algorithms regarding the timing of AVR in asymptomatic patients. Biomarkers may complement echocardiographic indices of LV remodeling to identify patients with a more maladaptive response to pressure overload, which may become irreversible if valve replacement is delayed. Several attempts have been made to identify biomarkers of AS severity that could be used to refine AS risk stratification, improve early detection of cardiac decompensation, and lead to timely AVR. The present report will systematically review the current literature on biomarkers in AS. The search strategy is outlined in Supplemental Table 1 (available online).

Pathophysiology in AS

Each biomarker discussed in this review reflects an underlying pathological process within the aortic valve and/or adjacent heart structure (Figure 1; Supplemental Table 2, available online). We therefore provide a brief overview of the pathological processes that occur in AS. For a thorough review of the pathophysiology in AS, the reader is referred to an extensive review by Lindman and colleagues.[35]

At the level of the valve, endothelial damage allows infiltration of lipids, specifically low-density lipoprotein (LDL) and lipoprotein(a) (Lp(a)) into the fibrosa and triggers the recruitment of inflammatory cells into the aortic valve.[36–38] Inflammatory cells such as macrophages and lymphocytes that have been recruited to the fibrosa release inflammatory cytokines and matrix

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Table 1. Studies evaluating B-type natriuretic peptides in aortic stenosis.

Authors	Year	*N*	Restricted to severe AS	Population	Findings
Gerber et al.[50]	2003	74	No	Vmax >2.5 m/s No segmental wall motion abnormality	NTproBNP and BNP both associate with symptoms (AUC 0.84 and 0.83)
Bergler-Klein et al.[49]	2004	130	Yes	Vmax >4 m/s and/or AVA <1.0 cm^2	NTproBNP and BNP both predicted the presence of symptoms as well as the risk of symptom onset or death 12-month event rate was 31% (NTproBNP <80 pmol/L) vs. 92% (NTproBNP ≥80 pmol/L)
Lim et al.[51]	2004	70	Yes	AVA <1.0 cm^2 Normal LV function	BNP predicts presence of symptoms (AUC 0.86) and independently predicts cardiovascular death
Weber et al.[47]	2004	146	No	Degenerative AS (any severity)	NTproBNP predicted severity of AS and predicted occurrence of AVR (AUC 0.73)
Gerber et al.[141]	2005	29	No	Asymptomatic Vmax ≥2.5 m/s No segmental wall motion abnormality or concomitant valve disease	NTproBNP predicted symptoms (cutoff 50 pmol/L)
Nessmith et al.[48]	2005	124	No	AVA <1.2 cm^2	BNP predicted presence of symptoms (AUC 0.87) Optimal cutoff was 190 pg/mL
Weber et al.[142]	2006	102 (57[a])	No	Mild, moderate, or severe AS	NT-proBNP independently predicted outcome (death or hospitalization for AS)
Feuchtner et al.[143]	2006	34	No	Asymptomatic degenerative AS	BNP predicted MACE, defined as symptom onset or mortality
Antonini-Canterin et al.[73]	2007	64	No	Isolated aortic stenosis	BNP predicted NYHA class III–IV status (AUC 0.78) and event-free survival (cardiac death, AVR, hospitalization for CHF)
Dichtl et al.[11]	2008	50	No	Asymptomatic ΔP ≥15 mm Hg, Vmax ≥2 m/s, and aortic valve calcification	NTproBNP predicted MACE (cardiac death, symptoms onset, acute coronary syndrome, or endocarditis)
Van Pelt et al.[144]	2008	34	No	Asymptomatic Moderate or severe AS (Vmax >3 m/s)	BNP predicts abnormal blood pressure response on exercise
Poh et al.[145]	2008	53	No	Variable degrees of AS Sinus rhythm and LVEF >50%	NT-proBNP predicted outcome (cardiac death or symptom-driven AVR)
Monin et al.[146]	2009	107	No	Asymptomatic Moderate to severe AS (Vmax ≥3.0 m/s OR AVA ≤1.5 cm^2)	BNP independently predict outcome (cardiac death, hospitalization for CHF or AVR)
Lancelotti et al.[52]	2010	126	No	Asymptomatic Moderate to severe AS (AVA ≤1.2 cm^2) LVEF ≥55%, Sinus rhythm	BNP predicted outcome (cardiac death, symptoms or AVR) AUC 0.89, Best cutoff was 61 pg/mL
Katz et al.[147]	2012	64 (13[a])	Yes	Severe AS	BNP and NT-proBNP were both independently associated with mortality over a mean follow-up period of 1520 ± 681 days.
Ben-Dor et al.[56]	2013	289	Yes	High risk severe AS referred to TAVR	BNP predicted outcome in univariate but not in multivariable analyses (included variables not presented)
Cimadevilla et al.[57]	2013	361	No	Patients older than 70 years with AS	BNP correlated with severity (AUC = 0.73). BNP predicted symptom free survival in univariate but not multivariable (adjusted for age, AVA, and sex) model
Capoulade et al.[53]	2014	211	No	Asymptomatic Moderate to severe AS (Vmax >2.5 m/s AND AVA <1.5 cm^2) Preserved LVEF 157 patients had severe AS	Both baseline BNP and peak BNP during exercise were associated with outcome (death, symptom/LVEF-driven AVR)
Clavel et al.[55]	2014	1,923	No	Moderate or severe AS	BNP ratio (defined as measured BNP/maximal normal BNP specific to age and sex) independently predicted survival
Farre et al.[54]	2014	237	No	Asymptomatic Moderate or severe degenerative AS (Vmax >3.5 m/s and/or AVA <1.25 cm^2)	NT-proBNP predicted outcome (hospitalization for angina, syncope, or CHF; AVR; or death)
Henri et al.[148]	2015	69	No	Asymptomatic Moderate or severe AS (AVA <1.5 cm^2) LVEF >50%	Annual change in BNP levels predicted outcome (symptoms, AVR, or death)
O'Neil et al.[58]	2015	933	Yes	Symptomatic from PARTNER AVA ≤0.8 cm^2 AND Vmax ≥4 m/s or ΔP ≥40 mm Hg	Baseline BNP predicted death after TAVR
Abramowitz et al.[59]	2016	780	Yes	Severe AS Compared low, medium, and high baseline BNP tertiles	Baseline BNP predicted death after TAVR. Median follow-up was 13.1 years. 62 patients died during the first 6 months
Goodman et al.[61]	2016	530	No	Moderate or severe AS (AVA <1.3 cm^2) and normal LVEF	Baseline BNP predicted death in multivariable models and added value over left ventricular strain 161 patients died (30%) during a mean follow-up of 4.7 ± 2 years. 76% underwent TAVR during the study duration
Koskinas et al.[60]	2016	340	Yes	Severe AS who underwent TAVR	Baseline BNP predicted death after TAVR

Note. [a]Number of conservatively managed patients.

ΔP, pressure difference across the aortic valve; AS, aortic stenosis; AUC, area under the curve; AVA, aortic valve area; BP, blood pressure; CHF, congestive heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; RWT, relative wall thickness; Vmax, maximum Doppler velocity signal across the aortic valve.

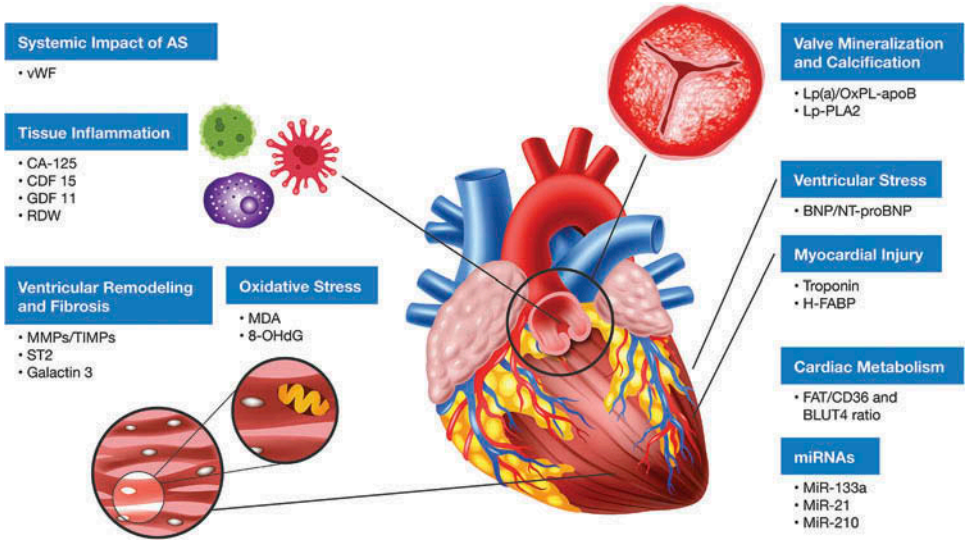

Figure 1. Pathophysiological processes involved in aortic stenosis and associated with biomarkers.

metalloproteinases, leading to degradation of cusp collagen and proteoglycans.[39–42] These biological events lead to osteoblastic transition of valve interstitial cells and active cusp calcification.[37,38] As a result, with time the calcified valve becomes increasingly rigid and stenotic.

The stenotic aortic valve increases the resistance that the left ventricle (LV) must overcome during systole, i.e. the LV afterload. The LV initially responds through myocardial remodeling, which allows for the restoration of wall tension, an important determinant of cardiomyocyte oxygen consumption, by undergoing concentric hypertrophy (wall thickening) in accordance with LaPlace's law

$$\sigma = [P \; x \; r] \; / 2h$$

where σ is LV wall tension, P is LV pressure, r is LV radius, and h is myocardial wall thickness. LV hypertrophy compensates for increased luminal pressure and normalizes myocardial wall tension but becomes maladaptive with time, so-called adverse cardiac remodeling.[43] The precise mechanisms behind the transition from adaptive to maladaptive hypertrophy are poorly defined but involve cardiomyocyte death and myocardial fibrosis.[44]

B-type natriuretic peptides

B-type natriuretic peptide (BNP) and its prohormone N-terminal pro B-type natriuretic peptide (NT-proBNP) are released in response to ventricular and/or atrial cardiomyocyte stretch.[45] The exact mechanisms behind the release of these biomarkers and how they relate to LV remodeling are incompletely understood; however, BNP levels have considerable prognostic value in patients with heart failure (HF).[45,46] Reports of NT-proBNP or BNP in AS are summarized in Table 1.

NT-proBNP levels correlate with AS severity, aortic valve area, peak velocity, peak transvalvular gradient, and echocardiographic markers of higher risk of adverse outcomes in AS.[45,47] In asymptomatic severe AS, baseline BNP levels are predictive of an abnormal blood pressure response to exercise, earlier symptom onset, and increased risk of re-hospitalization due to HF, need for AVR, and mortality.[48–52] Of note, most of these studies excluded patients with depressed LV function and/or concomitant valve disease which might otherwise cause elevated natriuretic peptide levels.[53,54] Hence, the results and conclusions of these studies apply to AS patients with otherwise normal cardiac structure and function. On the basis of these associations the European Society Cardiology/European Association for Cardio-Thoracic Surgery guidelines but not the AHA/ACC guidelines note that AVR may be considered in patients with asymptomatic severe AS and markedly elevated levels of natriuretic peptides in the absence of an alternative explanation (class IIb).[19,20] Although merely a class IIb recommendation, BNP is the only biomarker that is acknowledged by current guidelines to have an established prognostic value. A recent study showed that BNP activation, defined as the ratio between the measured BNP and the maximum expected BNP for a subject's age and sex, was a strong and persistent predictor of mortality.[55]

The predictive value of BNP may be lower in the elderly, the patient group most commonly affected by AS. Two studies that enrolled predominantly older patients (mean age 79.6 ± 6 years and 82.5 ± 8.4 years) have questioned the association between BNP and adverse outcomes in AS.[56,57] In these studies BNP levels were associated with AS severity and outcomes in a univariate analysis but not after multivariable adjustment.

Importantly, recent reports have shown that baseline BNP is predictive of worse outcomes among patients who undergo TAVR.[58–61] These observations are consistent across most reports and remain significant after multivariable adjustment. This implies that markedly elevated BNP levels may reflect irreversible damage to the myocardium. If this is the case, then deferring AVR in patients with asymptomatic AS until BNP levels rise markedly may not be optimal. Instead, more sensitive markers that allow for earlier intervention may be preferable.

Markers of myocardial injury

Cardiac troponins

Troponin I and Troponin T are cardio-specific components of the cardiomyocytes' contractile apparatus. Elevated cardiac troponins in serum have been thought to reflect cardiomyocyte necrosis with degradation of the contractile filaments; however, cardiac troponins also exist in cytosolic pools and can be released in smaller amounts when the integrity of the cell membrane is compromised in response to sub-lethal damage.[62] Studies evaluating cardiac troponins in AS are summarized in Table 2. Plasma troponin I concentrations have been shown to be associated with increased LV mass and fibrosis, as assessed by magnetic resonance imaging.[63] Although the data are less robust compared to BNP, particularly among patients with asymptomatic severe AS, baseline troponin levels are predictive of worse outcomes in patients with severe AS. This appears to hold true regardless of whether the patients are treated conservatively or undergo TAVR or SAVR.[64–66] As was the case with BNP, the independent association between baseline troponin levels and worse prognosis after AVR implies that elevated troponins in AS are reflective of irreversible remodeling processes and that intervention before the onset of adverse remodeling, or early in its course, may improve prognosis after AVR.

Heart-type cytosolic fatty acid binding proteins (H-FABP)

H-FABP is another fatty acid transporter that is proven to be closely related to myocardial injury in patients with acute coronary syndromes[67] and/or HF.[68] H-FABP levels correlated with relative wall thickness in a cohort of patients with mild to moderate AS and were an independent predictor of cardiac events after adjustment for indices of LV function.[69]

Biomarkers related to tissue inflammation

Several biomarkers related to local and/or systemic inflammatory processes have been studied in the setting of AS (Table 3).

Cancer antigen 125 (CA-125)

CA-125 is released from mesothelial cells in response to either pro-inflammatory cytokines or serosal effusions and is associated with disease progression and clinical outcomes in patients with HF.[70,71] CA-125 levels are associated with the presence of symptoms and increased risk of adverse events and appears to have incremental value over BNP, the logistic EuroSCORE, and New York Heart Association Class.[72,73] CA-125 also correlates with echocardiographic measures of LV and atrial size and function, and appears not to be influenced by renal function, age, or body mass index.

Growth differentiation factor 15 (GDF-15)

GDF-15 is a stress-responsive cytokine belonging to the transforming growth factor family that participates in inflammation and apoptotic pathways.[74,75] Higher levels are associated with worse outcomes in HF patients.[76] GDF-15 has been shown to be superior to NT-proBNP for predicting risk in patients undergoing TAVR and added incremental value over

Table 2. Studies evaluating markers of cardiac injury in aortic stenosis.

Authors	Year	*N*	Restricted to severe AS	Population	Findings
Cardiac Troponin					
Rosjo et al.[149]	2011	57	No	Patients with AS and LV hypertrophy. 30 patients had SAVR.	Baseline troponin levels predicted degree of LV hypertrophy and predicted mortality.
Solberg et al.[150]	2012	136	No	Patients with AS (mean valve area 0.62 cm^2) who were either treated conservatively or underwent SAVR.	Baseline troponin predicted mortality. A combination of troponin and NT-proBNP improved prediction.
Saito et al.[151]	2013	60	Yes	Patients who underwent SAVR due to severe AS. Most were symptomatic	Baseline troponin predicted death in univariate analysis. Multivariable analysis was not performed.
Frank et al.[152]	2013	107	No	Patients with AS who underwent TAVR.	Baseline troponin independently predicted survival in patients undergoing TAVR.
Chorianopoulos et al.[66]	2013	198	Yes	Patients with symptomatic severe AS who underwent TAVR.	Baseline troponin predicted mortality.
Chin et al.[63]	2013	122 + 131	No	Patients with AS (mean AVA 1.0 ± 0.4 cm^2) Two separate cohorts: "Mechanism Cohort" (n = 122) and "Outcomes Cohort" (n = 131)	Higher plasma TNI concentrations were associated with increased hypertrophy and replacement fibrosis. Higher plasma TNI concentrations were associated with higher adjusted risk of AVR or death.
Lindman et al.[64]	2015	345	Yes	Patients with severe AS (AVA <1.0 cm^2) who were referred for and treated with AVR (TAVR [n = 183] or SAVR [n = 162])	Baseline troponin predicted death in univariate but not multivariable analyses.
Kohler et al.[65]	2016	267	No	Patients with AS undergoing TAVR Mean age 82 ± 6 years	Baseline troponin predicted death in univariate and multivariable analysis (multivariable model not presented).
Heart-type Cytosolic Fatty Acid Binding Proteins					
Iida et al.[69]	2007	285 (73 with AS)	No	Patients with mild to moderate AS (mean valve gradient 25 ± 11.7) or mild-moderate AR or hypertensive cardiomyopathy.	H-FABP was independently correlated with RWT in AS (p < 0.05), and an independent predictor of cardiac events including worsening of heart failure, angina pectoris and cardiac death in AS (RR = 13.6, 95% CI = 3.27–66.9).

Note. ΔP, pressure difference across the aortic valve; AS, aortic stenosis; AUC, area under the curve; AVA, aortic valve area; BP, blood pressure; CHF, congestive heart failure; H-FABP, heart-type cytosolic fatty acid binding protein; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; Vmax, maximum Doppler velocity signal across the aortic valve.

Table 3. Studies evaluating other biomarkers in aortic stenosis.

Authors	Year	*N*	Restricted to severe AS	Population	Biomarker(s)	Findings
Biomarkers Related to Tissue Inflammation						
Antonini et al.[73]	2007	64	No	Any AS severity (mean AVA 0.92)	CA-125	Levels of CA-125 were significantly higher in more symptomatic (NYHA III-IV) vs. less symptomatic patients. CA-125 and BNP were both significantly correlated with several echocardiographic indices of left ventricular size and function. Both CA-125 and BNP levels were predictors of outcome (cardiac death, urgent AVR, or hospitalization for congestive heart failure). 52% of patients with CA-125 ≥10.3 U/mL vs. 13% with CA-125 <10.3 U/mL ($p = 0.01$) and 65% patients with BNP ≥254 pg/mL vs. 7% with BNP <254 pg/mL ($p < 0.001$) reached the end point.
Husser et al.[72]	2013	228	No	TAVR patients (93% AS, 6% degenerated bioprosthesis, 2% severe AI)	CA-125	A 3-fold increase in the rates for death and MACE was observed in patients with plasma CA-125 above vs. below the median (17 U/mL; 5.2 vs. 1.6 per 10 person-years and 8.3 vs. 3.3 per 10 person-years, respectively; $p < 0.001$ for both). In the multivariable analysis, baseline CA-125 remained independently associated with an increased risk of all-cause death (HR 2.18; 95% CI 1.11–4.26; $p = 0.023$) and MACE (HR 1.77; 95% CI 1.05–2.98; $p = 0.031$).
Aung et al.[79]	2013	175	—	Patients undergoing TAVR	RDW	On multivariable survival analyses, baseline RDW ≥15.5% independently predicted death (adjusted HR 2.70, 95% CI 1.40–5.22, $p = 0.003$). A greater rate of increase in RDW over time was independently associated with increased mortality (adjusted HR 1.11; 95% CI 1.04–1.18, $p = 0.001$) with an increase in RDW >0.1%/month being associated with a 2-fold increased risk of mortality.
Sinning et al.[74]	2015	310	Yes	Patients undergoing TAVR	GDF-15	Among the measured biomarkers GDF-15 was the strongest predictor for 1-year mortality (AUC 0.686) and added to incremental value to the logistic EuroSCORE and EuroSCORE II score, as assessed by reclassification indices.
Krau et al.[75]	2015	217	Yes	Patients undergoing TAVR (mean AVA 0.7 cm^2)	GDF-15	GDF-15 levels in the upper fourth quartile showed a significant association with reduced survival time after TAVR ($p < 0.001$). Patients with GDF-15 levels in the upper quartile had increased mortality risk compared to patients with GDF-15 levels in the lower three tertiles (HR 2.40; 95% CI 1.47–3.93, $p < 0.001$). NT-proBNP did not remain significantly associated with mortality when adjusted for GDF-15.
Lindman et al.[64]	2015	348	Yes	Patients undergoing TAVR or AVR	GDF-15	GDF-15 was found to be predictive of mortality in unadjusted (HR 1.89; 95% CI 1.54–2.31) and adjusted for clinical factors (HR 1.61; 95% CI 1.28–2.03) and STS score (HR 1.71; 95% CI 1.36–2.13).
Schafer et al.[78]	2016	73	Yes	Patients undergoing TAVR or SAVR	GDF-11	GDF-11 was independently associated with frailty (adjusted $p = 0.003$). Associations between GDF-11 and rehospitalization ($p = 0.044$) or multiple adverse post-operative events ($p = 0.041$) also remained statistically significant after adjusting for potential confounding demographic and comorbidity variables.
Markers of Oxidative Stress						
Parenica et al.[39]	2012	42	Yes	SAVR and TAVR (mean AVA 0.6 cm^2)	MDA	MDA was the strongest predictor of the combined VARC endpoint[a] at 1 year (AUC = 0.872 for the TAVR group). Increased levels of MDA, MMP2, TIMP1, and 8-hydroxy-2-deoxyguanosine were all predictors of the occurrence of the VARC combined safety endpoint[a] at 30 days. The addition of MDA to the EuroSCORE model significantly improved the prediction of VARC combined safety endpoint[a] at 30 days and VARC combined endpoint (0–365 days) ($p < 0.05$).
Markers-Related Ventricular Remodeling						
Baldenhofer et al.[109]	2014	101	Yes	Patients undergoing TAVR (mean AVA 0.73 cm^2)	Galectin-3	Galectin-3 was independently associated with increased risk for reaching the 30-day VARC safety endpoint[a] in a Cox proportional hazards model (HR 3.36; 95% CI 1.47–7.69; $p = 0.004$), of death (HR 4.48; 95% CI 1.56–12.91; $p = 0.005$). Galectin-3 was also an independent predictor of cardiovascular events (defined as any cardiovascular death, non-fatal myocardial infarction, stroke, or transient ischemic attack; HR 5.12; 95% CI 2.10–12.47; $p < 0.001$). Combination of galectin-3 with NT-proBNP resulted in incremental prognostic information.
Kapelouzou et al.[42]	2015	60	Yes	Patients undergoing SAVR (AVA 0.5–0.9 cm^2)	TIMP1, MMP2, MMP9	TIMP1/MMP2 and TIMP1/MMP9 ratios differed considerably between SAVR patients and healthy controls. MMP2, MMP9, and MDA levels were higher in SAVR patients compared to the control group ($p = 0.03$, $p < 0.0001$, and $p < 0.0001$ respectively). The extent of valve calcification as evaluated by alizarin red was positively correlated with TIMP1 ($r = 0.304$, $p = 0.01$), MCP-1 ($r = 0.296$, $p = 0.02$), and negatively correlated with MMP-9 ($r = -0.325$, $p = 0.01$).
Lancelotti et al.[105]	2015	86	No	Moderate or severe AS with preserved LVEF (>50%)	sST2	sST2 (>23 ng/mL, AUC = 0.68, $p < 0.01$) was more accurate than BNP in identifying patients who would develop symptoms during follow-up. sST2 level was an independent predictor of cardiovascular events, defined as death, dyspnea, acute pulmonary edema.
Lindman et al.[64]	2015	348	Yes	Patients undergoing TAVR or AVR	sST2	sST2 was found to be predictive of mortality in unadjusted (HR 1.55; 95% CI 1.26;1.91) and adjusted for clinical factors (HR 1.45; 95% CI 1.16–1.81) and STS score (HR 1.37; 95% CI 1.10–1.70).

(*Continued*)

Table 3. Studies evaluating other biomarkers in aortic stenosis. (*Continued*).

Authors	Year	*N*	Restricted to severe AS	Population	Biomarker(s)	Findings
Markers Related to Valve Mineralization and Calcification Process						
Capoulade et al.[114]	2015	220	No	Mild or moderate AS	OxPL-apoB	AS progression was faster in the tertile of patients who had the highest plasma levels of lipoprotein a (peak aortic jet velocity: +0.26 ± 0.26 vs. +0.17 ± 0.21 m/s/y; $p = 0.005$) and OxPL-apoB (+0.26 ± 0.26 m/s/y vs. +0.17 ± 0.21 m/s/y; $p = 0.01$). Compared to patients in the lower two tertiles patients in the top tertile of lipoprotein a or OxPL-apoB had increased risk of AVR and cardiac death.
Capoulade et al.[115]	2015	183	No	Asymptomatic AS, AVA 1.24 cm^2	Lp-PLA2	Patients with increased Lp-PLA2 activity had a nonsignificant trend for faster AS progression rate than patients who did not have increased Lp-PLA2 activity (annualized Vpeak 0.17 ± 0.23 m/s/y vs. 0.12 ± 0.18 m/s/y, $p = 0.14$). There was a significant interaction between Lp-PLA2 activity and baseline AS severity on AS progression rate (i.e. interaction *p*-values were <0.05 for Vpeak, ΔP, and AVAi). In patients with mild AS (defined as Vpeak <3.0 m/s, $n = 123$) stenosis progression rate was 2-fold faster in the subset of patients with increased Lp-PLA2 activity (annualized progression of Vpeak 0.16 ± 0.18 m/s/y vs. 0.09 ± 0.14 m/s/y, $p = 0.01$). On multivariable analysis Lp-PLA2 activity was independently associated with a faster annualized progression rate of Vpeak ($p = 0.005$), ΔP ($p = 0.02$), or AVAi ($p = 0.02$) in the subset of patients with mild AS.
Markers of Alterations in Cardiac Metabolism						
Heather et al.[117]	2011	18	No	Patients undergoing SAVR	FAT/CD36 GLUT4	With increasing cardiac hypertrophy there was a shift from FAT/CD36 and electron transport chain complex I protein expression toward GLUT4 protein expression in the ventricle.
MicroRNAs as Potential Biomarkers in AS						
Rosjo et al.[124]	2014	57 AS, 10 control	Yes	Severe AS (AVA 0.7 cm^2)	miR-210	The prognostic accuracy of miR-210 for all-cause mortality was comparable to the accuracy of NT-proBNP levels: AUC = 0.64 (95% CI 0.50–0.76) vs. AUC = 0.67 (0.53–0.79), respectively, $p = 0.83$.
Other Biomarkers						
Vincentelli et al.[128]	2003	50	No	Severe ($n = 42$) and moderate AS ($n = 8$)	vWF	Mean ΔP correlated inversely with plasma vWF multimers ($r = -0.56$, $p < 0.001$), and plasma vWF levels improved after AVR. Bleeding episodes within the preceding 6 months were common among the study cohort (9 out of 20), with most cases being mucosal bleeding.
Blackshear et al.[153]	2013	66	No	Severe ($n = 30$), moderate ($n = 20$), or mild ($n = 16$) AS	vWF	Reduced levels of vWF multimers were associated with mean ΔP and an increased risk of the composite of death ($n = 4$) or AVR ($n = 22$).
Spangenberg et al.[129]	2015	95	Yes	Severe AS undergoing TAVR	vWF	Abnormal vWF multimers, defined as a densitometric high-molecular-weight multimer (HMWM) content of <20.4%, were common (42%) but improved after TAVR. Paravalvular leak after TAVR was associated with less pronounced improvement in HMWM. Pre-procedure mean ΔP correlated inversely with pre-procedure HMWM.
van Belle et al.[154]	2015	30	Yes	Severe AS undergoing TAVR ($n = 20$) or BAV ($n = 10$)	vWF	Plasma vWF was reduced in the patient cohort at baseline but increased considerably after TAVR but not BAV.
van Belle et al.[131]	2016	183	Yes	Severe AS undergoing TAVR	vWF	Plasma levels of vWF was reduced in patients with AS and normalized post TAVR only in patients without ($n = 137$) aortic regurgitation post-implantation. Plasma levels of vWF post-TAVR were independently associated with increased mortality at 1 year.
Multi-Marker Approach						
Lindman et al.[64]	2015	345	Yes	AVA <1.0 cm^2	GDF-15, sST2, NT-proBNP	The number of elevated biomarkers (GDF-15, sST2, and NT-proBNP) was associated with higher mortality post TAVR/SAVR (adjusted HR 2.95 and 4.3 for 2 and 3 elevated biomarkers, respectively).

Note. [a]VARC combined endpoint is defined as the composite of all-cause mortality, major stroke, life-threatening [or disabling] bleeding, acute kidney injury requiring renal replacement therapy, peri-procedural myocardial infarction, any major vascular complication, and re-intervention for valve-related dysfunction [either surgical or interventional].

ΔP, pressure difference across the aortic valve; AI, aortic insufficiency; AS, aortic stenosis; AUC, area under the curve; AVA, aortic valve area; AVAi, aortic valve area index; AVR, aortic valve replacement; BAV, balloon aortic valvuloplasty; BNP, B-type natriuretic peptide; CA 125, cancer antigen 125; CD36, cluster of differentiation 36; FAT, fatty acid translocase; GDF, Growth Differentiation Factor; GLUT4, glucose transporter type 4; HR, hazard ratio; Lp-PLA2, lipoprotein-associated phospholipase A2; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MDA, malonaldehyde; MMP, matrix metalloproteinase; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OxPL-apoB, oxidized phospholipids on apolipoprotein B; ROC, receiver operating characteristic; RDW, red cell distribution width; SAVR, surgical aortic valve replacement; sST2, soluble ST2; TAVR, transcatheter aortic valve replacement; TIMP, tissue inhibitors of matrix metalloproteinase; VARC, Valve Academic Research Consortium; Vpeak, maximum Doppler velocity signal across the aortic valve; vWF, von Willebrand factor.

the logistic EuroSCORE.[64,75] GDF-15 is associated with extracardiac disease, making it less AS-specific but potentially useful for overall risk stratification.[74]

Growth differentiation factor 11 (GDF-11)

GDF-11 is another newly discovered member of the transforming growth factor family that may be useful for predicting risk in AS. GDF-11 is believed to be involved in "aging processes" and to be reflective of frailty.[77,78] GDF-11 levels are predictive of post-operative complications and re-hospitalizations after AVR.[78]

Red blood cell distribution width (RDW)

RDW is increased among patients with inflammatory conditions, renal dysfunction, atherosclerosis, and states of ineffective erythropoiesis.[79–81] RDW expansion is associated with progression of HF and worse prognosis.[82–84] RDW at baseline is associated with increased mortality after TAVR, and expanding RDW during patient follow-up predicts mortality independent of baseline RDW.[79]

Markers of oxidative stress

Oxidative stress is closely related to inflammation and is an important component in the pathophysiology of various cardiovascular diseases, including AS.[85,86] Oxidative stress, through the production of lipid peroxides and free radicals, damages cell components including proteins, lipids, and DNA.[85,86]

Malondialdehyde (MDA)

MDA is a highly reactive product of lipid peroxidation and among the most studied markers of oxidative stress.[87] MDA levels appear to be increased in patients with AS and were shown to be predictive of worse outcomes, including increased risk of dying after TAVR.[39,42] In these studies, MDA levels provided incremental value over the EuroSCORE for risk prediction.

8-hydroxy-2-deoxyguanosine (8-OHdG)

Another marker of oxidative stress that may be useful for risk prediction in AS is 8-OHdG, a product of DNA oxidation. Higher levels of 8-OHdG were associated with higher rates of achieving the Valve Academic Research Consortium combined safety endpoint at 30 days (which includes all-cause mortality, major stroke, life-threatening [or disabling] bleeding, acute kidney injury requiring renal replacement therapy, peri-procedural myocardial infarction, any major vascular complication, and re-intervention for valve-related dysfunction [either surgical or interventional])[88] in both TAVR and SAVR patients.[39]

Markers of ventricular remodeling

Markers of extracellular matrix metabolism

The maladaptive response of the LV in AS involves remodeling of the extracellular matrix with deposition of interstitial collagen, leading to myocardial fibrosis and increased myocardial wall stiffness.[40] Interstitial fibrosis can be detected in patients with AS before any signs of impaired cardiac function can be detected by echocardiography. Several biomarkers have been identified that reflect extracellular matrix remodeling. These include transforming growth factor β1,[40,42,89] collagen-derived peptides,[90] matrix metalloproteinases (MMPs), and tissue inhibitors of MMPs (TIMP).[39–42] Both TIMP1 and MMP2 appear to have incremental value over established clinical risk models for prediction of the Valve Academic Research Consortium combined safety endpoint at 30 days after TAVR, while MMP2 also improved the prediction of a combined endpoint (defined as the occurrence of any clinical [safety or efficacy] endpoint, wherein efficacy includes all-cause mortality after 30 days, hospitalization for symptoms of valve-related or cardiac decompensation, and prosthetic heart valve dysfunction) throughout 1 year of follow-up.[39] Important limitations of these biomarkers include uncertainties in regard to their specificity for cardiac disease[91–94] and their route of clearance. There also appears to be considerable variability between the different assays in the results reported.[95,96]

ST2

ST2 is a member of the interleukin (IL)-1 receptor family with membrane-bound (ST2L) and soluble (sST2) forms. The soluble form of ST2 is thought to function as a decoy receptor, antagonizing the anti-hypertrophic and anti-fibrotic effects of IL-33.[97–99] Both cardiac fibroblasts and cardiomyocytes express IL-33 and sST2, and expression levels are increased in response to myocardial stress. sST2 concentrations have been shown to be increased after myocardial infarction as well as in acute HF and correlate with infarct size, degree of cardiac dysfunction, and hemodynamic and neurohormonal derangement.[100–102] In patients with AS, sST2 levels have been shown to correlate with echocardiographic indices of diastolic function and have been shown to predict symptom onset in asymptomatic patients with severe AS.[103–105] sST2 has also been shown to be a strong predictor of mortality after valve replacement.[64]

Galectin 3 (Gal-3)

Gal-3 is a member of the ß-galactoside binding protein family. It is expressed in a variety of cells, including leukocytes and fibroblasts, and participates in myocardial inflammation and fibrosis.[106–108] Gal-3 has been shown to be an independent predictor of mortality and added incremental value to NT-proBNP in one study[109] but was not an independent predictor of mortality in another.[64] An important limitation of Gal-3 is that it is not specific to cardiac conditions and is elevated in patients with reduced renal function.[110]

Markers related to valve mineralization and calcification process

Valve mineralization plays a central role in AS progression. It involves the accumulation of oxidized low-density lipoprotein cholesterol in the intima of the valve cusps.[111–113]

Lipoprotein-associated phospholipase A2 (Lp-PLA2)

Lp-PLA2 uses oxidized low-density lipoprotein cholesterol as substrate and produces free fatty acids and lysophosphatidylcholine, a powerful pro-inflammatory and pro-calcifying factor.[114] In a substudy of the PROGRESSA study Lp-PLA2 activity was found to correlate well with accelerated AS progression among patients with mild AS.[115]

Lipoprotein a (Lp[a])

Another example of the pathogenic role of oxidized lipoproteins was reported by Capoulade and coauthors,[115] who showed that oxidized phospholipids per apolipoprotein B-100 (OxPL-apoB) and its major plasma carrier Lp(a) correlated with disease progression and outcomes in a cohort of patients with mild-to-moderate AS. They found an independent correlation between the rate of AS progression and OxPL-apoB and Lp(a) levels. Patients with Lp(a) or OxPL-apoB levels in the highest tertile had increased risk of AVR and cardiac death after adjustment for other known risk factors.

Markers of alteration in cardiac metabolism

Under resting conditions, the normal heart derives approximately 70% of its energy from fatty acid oxidation. In the hypertrophied heart a greater proportion of the energy is derived from glucose.[116,117] Analyses of tissue from patients undergoing SAVR have shown that the abundance of the glucose transporter GLUT4 relative to the fatty acid transporter FAT/CD36 correlated with severity of LV hypertrophy.[117]

Micro RNA (miRNA) as a potential biomarker in AS

miRNA is small RNA that regulates gene expression by targeting mRNA for cleavage or translational repression.[118,119] These 19–25 nucleotide long non-coding RNA could function as "on/off switches" for various cellular functions and processes.[120] Circulating miRNA may be involved in critical biological processes underlying cardiovascular disorders and are currently being investigated as biomarkers in cardiovascular disease.[121] Examples of potential miRNA biomarkers in AS include miR-133a, which was shown to predict the extent of regression of LV hypertrophy after SAVR[122]; miR-21, which was shown to be associated with LV fibrosis[123]; and miR-210, which was independently associated with mortality in patients with moderate-to-severe AS.[124] miRNA research is expected to expand considerably in the coming years, and new candidate biomarkers will likely be identified.[121]

Other biomarkers

Biomarkers previously described mostly involved pathophysiological mechanisms directly or indirectly involved in the genesis of AS or underlying consequential cardiac cell injury. In addition, some biomarkers may reflect systemic consequences of AS. Acquired von Willebrand factor (vWF) deficiency, due to the molecular breakdown of the high molecular weight protein vWF in presence of AS, is one of the most clinically important examples.

vWF

vWF is a large multimeric glycoprotein present in blood plasma that plays a major role in secondary hemostasis. Under high shear stress conditions, such as high flow velocity due to AS, the conformational structure of vWF may change during aortic valve passage, triggering its cleavage (catabolic enzyme ADAMTS 13) and inactivation.[125–127] Proportional to the AS severity, plasma levels and function of vWF are reduced, which may result in clinically significant bleeding. The combination of gastrointestinal bleeding (intestinal angiodysplasia) and AS is a well-described entity (Heyde's syndrome).[128] Acquired vWF deficiency is also observed post-AVR in cases of significant paravalvular leak or prosthesis mismatch.[129–131] A recent study of 137 patients with AS showed that vWF normalized after TAVR in patients without significant paravalvular leak but did not normalize or partially normalize when post-implantation paravalvular leak was present.[131] This study further showed that reduced level of vWF was independently associated with increased mortality at 1 year. While these data suggest that vWF could be useful post-AVR to biologically detect the presence of high shear stress phenomena such as paravalvular leak, prosthesis–patient mismatch, or progressive re-narrowing of aortic prosthesis, whether vWF could be used as a surrogate marker of AS severity in order to help decide the appropriate timing of AVR remains to be demonstrated.

Incorporating biomarkers in clinical practice—a multi-modal and multi-marker approach

Since AS is a heterogeneous disease with a complex pathophysiology involving the aortic valve *per se* and interconnected cardiac structures, it is likely that the most effective risk stratification strategy is one that integrates the diversity of biological pathways involved in AS. Echocardiography paired with a careful clinical assessment of symptoms and functional limitation could be sufficient to appropriately risk stratify patients presenting with AS.[19,20] That being said, many patients with "echocardiographically defined" moderate AS or severe asymptomatic AS have an unfavorable prognosis when treated conservatively.[61,132,133] Pharmacologic testing (in low-flow/low-gradient AS) or exercise stress-testing (in severe asymptomatic AS) can effectively identify patients who are more likely to benefit from a strategy of early AVR compared to a watchful waiting strategy;[134] however, practically speaking, these two modalities require specific expertise, might not be suitable in a high proportion of patients (incapacity to perform stress test,

presence of baseline arrhythmia), and don't have perfect predictability.[134] Some clinicians might also be uncomfortable performing such tests among AS patients, which could explain the very low rate of adoption in daily practice.[61,132,133,135–140] While acknowledging their utility in risk stratification of patients with AS,[19,20] these limitations underscore the incremental value of more readily available screening tools such as blood biomarkers. Lindman and coworkers[64] recently reported that the risk of dying after TAVR increased with the number of elevated biomarkers and was 10-fold higher for patients with elevated GDF-15, sST2, and NT-proBNP compared to patients with no elevated biomarkers. Thus, a multi-pronged approach, including clinical, imaging, functional testing, and biochemical markers would be most likely to optimize risk-stratification of AS patients. Further research is needed to confirm the value and role in risk stratification of current and novel serum biomarkers in patients with AS. Prospective studies of biomarker-driven therapies in specific subsets of AS patients could provide a definite answer.

Potential opportunities for biomarkers to change clinical management—looking to the future

While all patients may not benefit from valve replacement before symptoms develop, asymptomatic patients with elevation of certain biomarkers or a certain number of biomarkers indicative of maladaptive remodeling may benefit from earlier valve replacement to optimize long-term cardiac performance.[64,108] Apart from a class IIb indication for AVR in patients with asymptomatic severe AS and markedly elevated BNP in the European guidelines, none of the reviewed biomarkers currently have an established role in risk-stratification or in guiding timing or type of AVR; however, upcoming randomized multicenter trials that will randomize patients to early valve replacement versus watchful waiting include pre-specified biomarker substudies that will shed further light on the role of biomarkers in risk stratification of patients with AS (NCT03042104).

Biomarkers have the potential to aid in the identification of patients at high risk for specific complications from valve replacement, including acute kidney injury, stroke, and valve thrombosis. Identification of high-risk subgroups would allow for testing of preventive measures specifically for patients who would be expected to benefit the most from these techniques.[64]

Biomarkers could help identify patients likely to have suboptimal outcomes with valve replacement alone, e.g. high early mortality, poor quality of life, and persistent heart failure. Adjunctive medical therapies could then be employed to optimize patient-oriented outcomes for these sub-populations.

Conclusions

Several biomarkers that reflect different pathological processes have been shown to have an incremental value over classic echocardiographic criteria and clinical assessment for risk-stratification of patients with AS. BNP is currently the only biomarker that is supported by guideline recommendations. While encouraging data seem to support a multi-marker approach for risk stratification of patients with AS, further validation is needed before it can be integrated in a future risk stratification algorithm for patients with AS.

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