

## **Blood biomarkers in left-sided valvular heart disease**

Augustin Coisne, Patrizio Lancellotti, Nancy Côté, Julien Ternacle, Sébastien Hecht, Julia Grapsa, Rebecca T Hahn, Marie-Annick Clavel, Mani A Vannan, Brian Lindman, Madalina Garbi, Cécile Oury, Erwan Donal, Andrea Scotti, Sebastian Ludwig, Adriana Postolache, Patrick Myers, Marc R Dweck, Philippe Pibarot

# Blood biomarkers in left-sided valvular heart disease

**Augustin Coisne** <sup>1,2,\*</sup>, **Patrizio Lancellotti**<sup>3,4</sup>, **Nancy Côté**<sup>5</sup>, **Julien Ternacle** <sup>6</sup>,  
**Sébastien Hecht**<sup>5</sup>, **Julia Grapsa** <sup>7</sup>, **Rebecca T. Hahn**<sup>8</sup>, **Marie-Annick Clavel** <sup>5</sup>,  
**Mani A. Vannan**<sup>9</sup>, **Brian Lindman** <sup>10</sup>, **Madalina Garbi**<sup>11</sup>, **Cécile Oury** <sup>3</sup>,  
**Erwan Donal** <sup>12</sup>, **Andrea Scotti** <sup>13</sup>, **Sebastian Ludwig** <sup>2,14</sup>,  
**Adriana Postolache**<sup>15</sup>, **Patrick Myers**<sup>16</sup>, **Marc R. Dweck**<sup>17</sup>, and **Philippe Pibarot** <sup>5</sup>;  
on behalf of the EuroValve Consortium

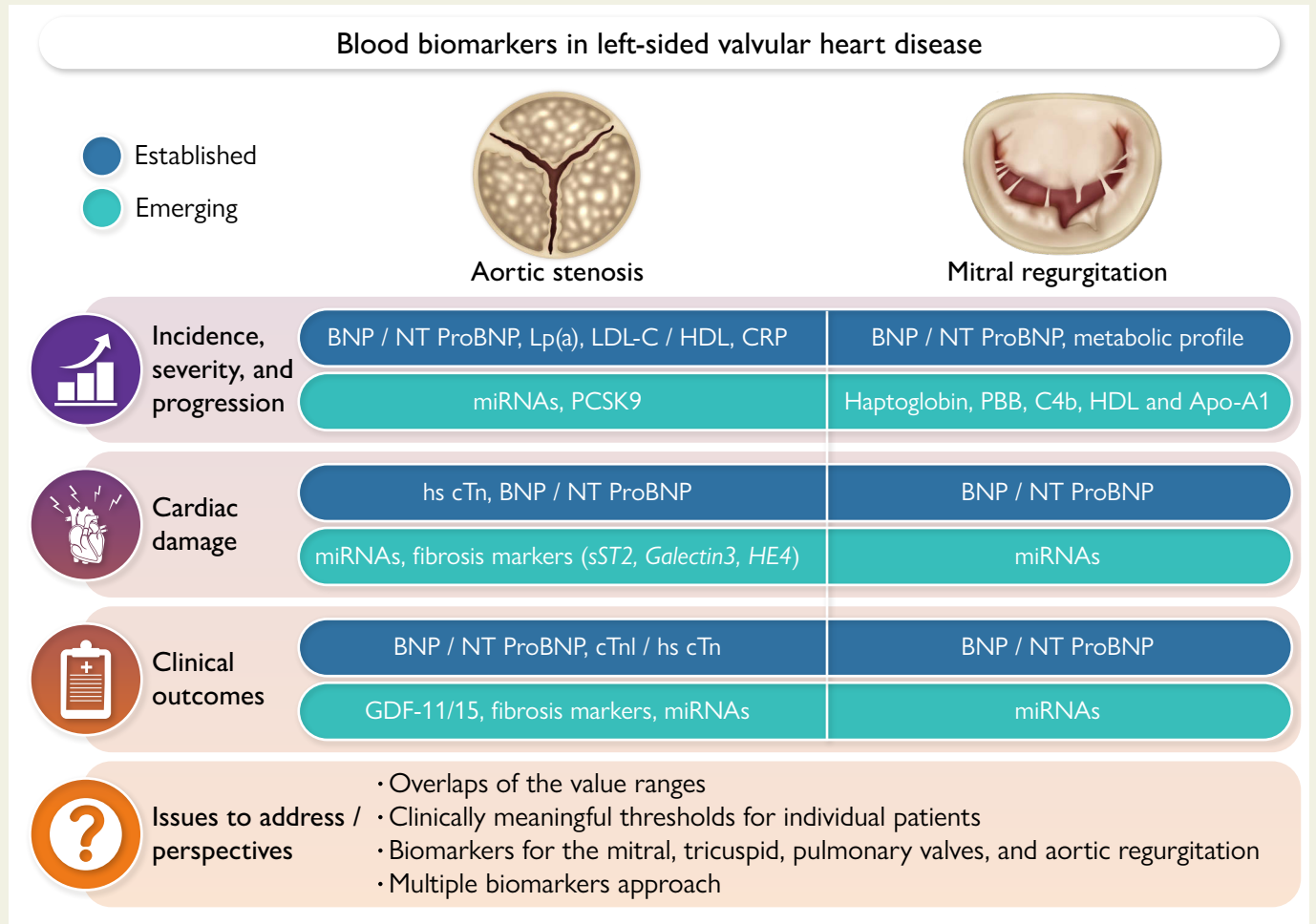
<sup>1</sup>Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011-EGID, Bd Pr Jules Ledercq, 59000 Lille, France; <sup>2</sup>Cardiovascular Research Foundation, New York City, NY 10019, USA; <sup>3</sup>GIGA Metabolism and Cardiovascular Biology, University of Liège, Liège, Belgium; <sup>4</sup>Department of Cardiology, Heart Valve Clinic, University Hospital CHU Sart Tilman, Liège B-4000, Belgium; <sup>5</sup>Institut Universitaire de Cardiologie et de Pneumologie de Québec (Quebec Heart and Lung Institute), Université Laval, Québec City, Québec, Canada; <sup>6</sup>Service Médico-Chirurgical: Valvulopathies-Chirurgie Cardiaque-Cardiologie Interventionnelle Structurale, Centre Hospitalier Universitaire Bordeaux, Bordeaux, France; <sup>7</sup>Guy's and St Thomas' NHS Trust Hospitals, London, UK; <sup>8</sup>Columbia University Medical Center/NY Presbyterian Hospital, New York City, NY 10032, USA; <sup>9</sup>Marcus Heart Valve Center, Piedmont Heart Institute, Atlanta, GA, USA; <sup>10</sup>Vanderbilt University, Nashville, TN, USA; <sup>11</sup>Royal Papworth Hospital, Cambridge University Health Partners, Cambridge Biomedical Campus, Cambridge, UK; <sup>12</sup>Cardiology Department, CHU de Rennes, Rennes, France; <sup>13</sup>Montefiore-Einstein Center for Heart and Vascular Care, Montefiore Medical Center, Albert Einstein College, Bronx, NY 10467, USA; <sup>14</sup>Department of Cardiology, University Heart & Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; <sup>15</sup>CHU UCL Namur- Site Godinne, Namur, Belgium; <sup>16</sup>Hôpital de LaTour, Meyrin, Switzerland; and <sup>17</sup>BHF Centre of Cardiovascular Science, The University of Edinburgh, Edinburgh, UK

Received 29 October 2024; revised 11 January 2025; accepted 20 March 2025; online publish-ahead-of-print 22 April 2025

\* Corresponding author. Tel: +33603811698, Fax: +33320444414, Email: [augustin.coisne@chu-lille.fr](mailto:augustin.coisne@chu-lille.fr)

© The Author(s) 2025. Published by Oxford University Press on behalf of the European Society of Cardiology. All rights reserved. For commercial re-use, please contact [reprints@oup.com](mailto:reprints@oup.com) for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

Graphical Abstract



Abstract

Valvular heart disease (VHD) is a common condition that poses several challenges from the standpoints of diagnosis and therapeutic management. While several studies have explored the role of blood biomarkers in assessing the severity and risk of progression of VHD, as well as in evaluating related cardiac damage and predicting the occurrence of adverse events, blood biomarkers are generally not considered criteria to trigger valve intervention in the latest European and American guidelines for VHD management. This review article provides an up-to-date overview of the utility of blood biomarkers to (i) assess the presence, severity, and progression of left-sided VHD; (ii) establish the presence and extent of cardiovascular damage; (iii) predict clinical outcomes before and after valve interventions; and (iv) identify patients at risk for early structural valve deterioration, valve thrombosis, and paravalvular leak.

**Keywords** Blood biomarkers • Valvular heart disease • Aortic stenosis • Mitral regurgitation • Tricuspid regurgitation

Introduction

Valvular heart disease (VHD) progression is unpredictable and varies considerably from one patient to another. There is currently no medical treatment that can halt, or at least, slow down the progression of VHD and the only treatment available for severe VHD is to repair or replace the valve. In asymptomatic patients with severe VHD, it remains unclear whether we should adopt a ‘watchful waiting’ strategy (i.e.

waiting for symptoms or left ventricular dysfunction) or propose an ‘early prophylactic’ intervention.<sup>1–3</sup> Several studies have explored the role of blood biomarkers in assessing the severity and risk of progression of VHD as well as evaluating related cardiac damage and predicting the occurrence of adverse events,<sup>4–7</sup> the vast majority focusing on left-sided VHD. Although blood biomarkers are generally not included as criteria to trigger valve interventions, the latest European and American guidelines give an IIa recommendation for aortic valve

replacement (AVR) in asymptomatic patients with severe aortic stenosis (AS) when B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) are markedly elevated (i.e. three-fold increase).<sup>1–3</sup>

The aim of this state-of-the-art review is to provide a current state of knowledge on the utility of left-sided blood biomarkers (*Graphical Abstract*) to (i) assess the presence, severity, and progression of VHD; (ii) establish the presence and extent of cardiovascular damage in these valvular conditions; (iii) predict clinical outcomes before and after valvular intervention; and (iv) identify patients at risk of early structural valve deterioration (SVD), valve thrombosis, and paravalvular leak (PVL).

## Biomarkers to assess the presence, severity, and progression of left-sided valvular heart disease

The identification of biomarkers of valve leaflet pathology has been challenging due to the limited availability of diseased tissues and knowledge about the pathophysiological mechanisms leading to the initiation and progression of VHD. Moreover, blood markers of inflammation, calcification, and fibrosis, the key processes that drive many heart valve disorders, usually reflect the activity of these processes in other more abundant tissues of the body. Therefore, most blood biomarkers used in the context of VHD typically reflect the effects of the valvular lesion—whether regurgitation, stenosis, or a combination of both—on the myocardium, through mechanisms like myocardial wall stress and remodelling. As such, the most commonly used blood biomarkers in clinical practice are the natriuretic peptides (BNP and NT-proBNP), which rise in response to cardiomyocytes stretch in pressure or volume overload conditions like aortic and mitral valve disease.<sup>8</sup> The pathophysiological mechanisms leading to VHD are exceedingly intricate, involving numerous signalling pathways and genetic factors, which hinder the development of effective pharmacotherapies. Additionally, accurately predicting the progression of VHD and determining the optimal timing for valvular intervention remain difficult. Identifying biomarkers associated with the incidence, severity, or progression of the disease is of paramount importance to improve therapeutic management of patients with VHD and even more in the context of AS to address the underutilization of AVR<sup>9–13</sup> or mitral valve surgery.<sup>14</sup>

### Aortic stenosis

The pathology of AS can be considered in two phases. The early initiation phase has many similarities to atherosclerosis with endothelial damage, lipid infiltration, and inflammation. Perhaps as a consequence, the risk factors for AS incidence demonstrate considerable overlap with atherosclerosis. The later propagation phase, however, differs from atherosclerosis with a self-perpetuating cycle of leaflet damage, fibro-calcific thickening, increased mechanical stress, and further leaflet damage driving disease progression. The factors associated with AS progression are different from those associated with its incidence, indeed the baseline degree of aortic valve calcification appears to be the strongest predictor of subsequent disease progression. An overview of blood biomarkers related to the incidence, severity, and progression of AS is provided in *Figure 1* and *Table 1*.

### Aortic stenosis incidence

Several studies have established a correlation between LDL cholesterol levels and the incidence of AS.<sup>19,20</sup> Aortic stenosis patients tend to

exhibit a higher level of small and dense LDL particles, suggesting that the phenotype of LDL particles may be more critical than LDL levels alone. These small and dense LDL particles are highly atherogenic, contribute to sustaining chronic inflammation, linger longer in circulation, and possess a greater capability to infiltrate tissues.<sup>53</sup>

The most studied and significant blood biomarker demonstrated to influence the occurrence of AS is lipoprotein(a) [Lp(a)]. Elevated Lp(a) levels and corresponding Lp(a) risk genotypes (rs10455872, rs3798220, kringle IV Type 2 repeat polymorphism) were associated with increased risk of AS in the general population, with levels >90 mg/dL predicting a three-fold increased risk.<sup>15</sup> However, this association was not confirmed in patients >70 years.<sup>16</sup> In two large prospective cohorts (EPIC-Norfolk and UK Biobank), high Lp(a) levels (>50 mg/dL) were associated with AS development risk.<sup>17</sup> The risk of AS also significantly increased upon genetically determined exposure to raised lipid levels, specifically LDL cholesterol, total cholesterol, and triglycerides.<sup>18</sup>

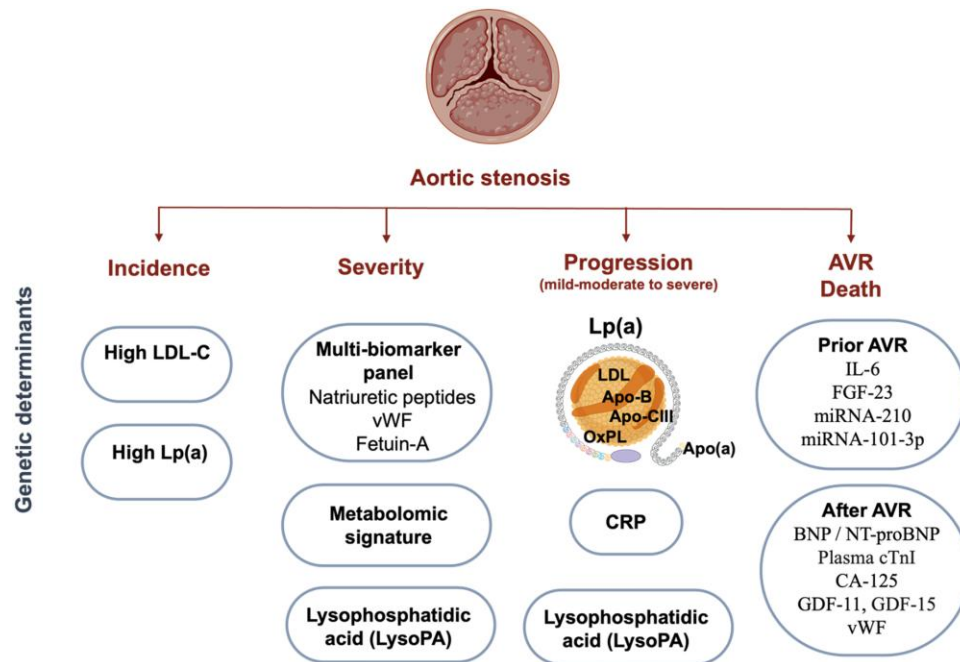
Accumulating evidence indicates that proprotein convertase subtilisin/kexin type 9 (PCSK9) may also contribute to incident aortic valve calcification. Increased plasma levels of PCSK9 correlates with the presence of AS while the loss-of-function variant PCSK9 R46L is associated with lower risk of aortic valve disease.<sup>21,22</sup> In the FOURNIER study, patients treated with PCSK9 inhibitors had a lower risk of AS or occurrence of AVR.<sup>23</sup> A recent *post hoc* analysis of this trial with evolocumab has brought attention to the reduction of Lp(a) as a potential therapeutic avenue for AS.<sup>23</sup> In this analysis, patients receiving evolocumab exhibited a lower incidence of new or worsening AS or AVR compared with those on placebo [.27% vs .41%; hazard ratio (HR), .48; 95% confidence interval (CI), .25–.93].

### Aortic stenosis severity

B-type natriuretic peptide plasma levels have long been associated with AS severity<sup>24</sup> and symptoms.<sup>25</sup> B-type natriuretic peptide plasma levels have also been reported to be higher in truly severe than in pseudo-severe low gradient AS.<sup>26</sup> However, BNP levels do not always reflect AS severity and may reflect a range of different co-morbidities affecting the myocardium, as well as age and sex. There is indeed a considerable overlap of these levels in the elderly population with and without AS.<sup>8</sup> Moreover, patients with discordant flow-gradient patterns (low flow/low gradient) may have lower BNP plasma levels than patients with either low-flow/high-gradient or normal-flow/high-gradient, despite markedly lower event-free survival.<sup>27</sup> Interestingly, studies in patients with heart failure have revealed that acute increases in BNP levels are often related to an impairment of its antioxidant effect, suggesting that BNP activity, rather than its plasma concentration, may be a more relevant parameter.<sup>54</sup>

Soluble ST2 (sST2), a circulating biomarker which is believed to reflect cardiovascular stress and increased myocardial fibrosis,<sup>55</sup> has been demonstrated to have a prognostic value in patients with heart failure.<sup>56,57</sup> A recent study, which included 86 patients with moderate to severe AS, reported a significant association between plasma levels of sST2 and symptom status and AS severity.<sup>32</sup> In addition, one study reported that elevated sST2 levels are associated with focal myocardial fibrosis and severe left ventricular hypertrophy,<sup>58</sup> while another study found no correlation between sST2 levels and myocardial fibrosis as assessed by biopsy of the interventricular septum.<sup>59</sup>

Recently, studies aimed at identifying blood-based biomarker panels, rather than isolated biomarkers, to improve diagnosis accuracy for severe AS. For instance, the CASABLANCA study developed a score of AS severity including age and concentrations of NT-proBNP, von



**Figure 1** Blood biomarkers of aortic stenosis incidence, severity, progression, and clinical outcomes. Apo-B, apolipoprotein-B; Apo-CIII, apolipoprotein-CIII; Apo(a), apolipoprotein(a); AVR, aortic valve replacement; AS, aortic stenosis; BNP, B-type natriuretic peptide; CA-125, cancer antigen 125; CRP, C-reactive protein; cTnI, cardiac troponin T; FGF-23, fibroblast growth factor 23; GDF-11, growth differentiation factor 11; GDF-15, growth differentiation factor 15; IL-6, interleukin-6; LDL-C, LDL cholesterol; Lp(a), lipoprotein (a); NT-proBNP, N-terminal pro-B-type natriuretic peptide; OxPL, oxidized phospholipids; vWF, von Willebrand factor

Willebrand factor (vWF), and fetuin-A.<sup>60</sup> In particular, severe AS can be complicated by chronic bleeding and thus anaemia, particularly that due to gastrointestinal angiodysplasia (Heyde's syndrome). This haemorrhagic syndrome is associated with acquired Type 2A von Willebrand syndrome, which is characterized by the loss of the largest multimers of vWF. The high shear stress induced by the severe AS leads to proteolysis and loss of high-molecular-weight multimers. Abnormalities of vWF are directly related to the severity of AS and are improved by valve replacement in the absence of prosthesis–patient mismatch or paravalvular regurgitation.<sup>61,62</sup> von Willebrand factor responds within minutes to any significant change in haemodynamic valve status, making it an accurate marker of the quality of surgical and transcatheter therapeutic interventions.<sup>63</sup> The limitation of the vWF as a biomarker is that its analysis cannot be obtained in real-time during the procedure. However, the quantification of the multimers structure of vWF by closure time of a membrane coated with collagen and adenosine-5'-diphosphate (CT-ADP) seems a reliable index of the presence and severity of several native or prosthetic valve dysfunction, which can easily and rapidly be measured during the procedure. C-reactive protein (CRP) has also been identified as a mechanosensitive protein that undergoes dissociation from a pentameric to a monomeric CRP conformation in response to the increase shear stress at the level of the stenotic aortic valve, which is associated with AS severity and progression rate.<sup>64</sup>

More recently, the analysis of serum metabolome revealed new markers of AS severity. A first study identified nitric oxide intermediates as the most distinctive markers of severe AS.<sup>33</sup> A second study showed altered metabolite profiles (acylcarnitine, ketone, and sugar metabolism) in AS patients compared with healthy controls, with bilirubin,

diacylglycerols, and dihydrosphingomyelins being differentially regulated among patients with different flow-gradient characteristics.<sup>34</sup> Another untargeted metabolomic approach including 37 229 metabolites indicated that the top three significantly altered metabolomics pathways associated with AS severity were the pathways involved in lipid metabolism and biosynthesis: glycerophospholipid metabolism, linoleic acid metabolism, and bile acid biosynthesis.<sup>35</sup> Among the various related lipid classes, lysophosphatidic acid (LysoPA) species showed a significant positive correlation with mean pressure gradient and maximum velocity and were independently associated with AS severity.

### Aortic stenosis progression

In the same study, the levels of LysoPA not only differed significantly between mild and severe AS, but elevated LysoPA levels were also associated with a faster AS progression rate.<sup>35</sup> Since LysoPA is the end product of Lp(a), this study extends the findings from the ASTRONOMER, the Ring of Fire, and SALTIRE I studies regarding the role of Lp(a) in AS haemodynamic progression.<sup>43,44</sup> In patients from the ASTRONOMER trial, elevated levels of apolipoprotein(Apo)CIII-Lp(a) complexes, in conjunction with Lp(a), OxPL-ApoB or OxPL-Apo(a) helped identify patients with pre-existing mild to moderate AS who displayed rapid progression.<sup>45</sup> In the Ring of Fire and SALTIRE studies, elevated Lp(a) levels were associated with increased calcification activity in the aortic valve, faster disease progression on echocardiography and CT calcium score as well as importantly more rapid progression towards the need for AVR.<sup>43,46</sup> A recent meta-analysis of five large trials confirmed that elevated Lp(a) was associated with faster haemodynamic AS progression on echocardiography.<sup>65</sup>

**Table 1** Blood biomarkers associated with presence, severity, myocardial consequences and progression in aortic stenosis

| Biomarker(s)                                                                         | Main findings                                                                                                                                                                                                      | Optimal cut-points | References |
|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------|
| Presence                                                                             |                                                                                                                                                                                                                    |                    |            |
| Lp(a)                                                                                | Three-fold increased risk of AS in the general population                                                                                                                                                          | >90 mg/dL          | 15,16      |
|                                                                                      | Increased risk of calcific aortic valve stenosis [HR (95% CI):1.86 (1.30–2.67)]                                                                                                                                    | > 50 mg/dL         | 17         |
| Lipid levels                                                                         | Risk of developing AS: [OR (95% CI): 1.52 (1.22–1.90); per .98 mmol/L for LDL-cholesterol, 1.03 (.80–1.31); per .41 mmol/L for HDL-cholesterol, and 1.38 (.92–2.07); per 1 mmol/L for triglycerides                | –                  | 18         |
| LDL-cholesterol                                                                      | Associated with the development of AS [OR (95% CI): 1.12 (1.03–1.23)]; $\pm$ 10-year increase                                                                                                                      | –                  | 19         |
| Total cholesterol                                                                    | Serum concentrations of total cholesterol are higher in patients with AS ( $P < .001$ )                                                                                                                            | –                  | 20         |
| PCSK9                                                                                | Old Pcsk9 <sup>-/-</sup> mice have lower aortic valve calcification                                                                                                                                                | –                  | 21         |
|                                                                                      | AS is less prevalent in carriers of the PCSK9 R46L variant [OR (95% CI): .80 (.70–.91); $P = .001$ ] and PCSK9 expression is higher in the aortic valves of AS patients                                            | –                  | 22,23      |
| AS severity and myocardial consequences                                              |                                                                                                                                                                                                                    |                    |            |
| BNP                                                                                  | Associated with AS severity and symptoms                                                                                                                                                                           | Three-fold         | 24–28      |
| NT-proBNP                                                                            | Increased levels in patients who developed symptoms compared with those who remained asymptomatic                                                                                                                  |                    | 29         |
| Hs cTnT                                                                              | Associated with LV mass and higher risk of AVR                                                                                                                                                                     |                    | 30         |
| Hs cTnl                                                                              | Plasma cTnl concentration is associated with advanced hypertrophy and replacement myocardial fibrosis as well as AVR or cardiovascular death [HR (95% CI): 1.77 (1.22–2.55)]                                       | –                  | 6,31       |
| sST2                                                                                 | Associated with AS severity and symptoms                                                                                                                                                                           | >23 ng/mL          | 32         |
| Nitric oxide                                                                         | Metabolites related to nitric oxide synthesis are higher in patients with AS before AVR compared with controls and show no reversal towards control values after AVR                                               | –                  | 33         |
| Bilirubin, diacylglycerols and dihydrosphingomyelins                                 | Differences between AS subtypes are found for metabolites belonging to haemoglobin metabolism, diacylglycerols, and dihydrosphingomyelins                                                                          | –                  | 34         |
| Glycerophospholipid metabolism, linoleic acid metabolism, and bile acid biosynthesis | The top 3 significantly alter metabolomics pathways associated with AS severity                                                                                                                                    | –                  | 35         |
| LysoPA                                                                               | Associated with AS severity                                                                                                                                                                                        | –                  | 35         |
| miRNAs                                                                               | miR-21: myocardial and plasma levels are significantly associated with higher LV fibrosis in AS patients compared with the controls and correlate directly with the echocardiographic mean transvalvular gradients |                    | 36         |
|                                                                                      | miR-22: highly expressed in calcified valve tissues and inhibition of miR-22 significantly negate the calcification process                                                                                        |                    | 37         |
|                                                                                      | miR-204: deficiency in diseased valves and in AV interstitial cells from diseased valves                                                                                                                           |                    | 38         |
|                                                                                      | miR-210: levels are two-fold increased in AS patients compared with controls ( $P = .002$ )                                                                                                                        |                    | 39         |
|                                                                                      | miR-378: lower levels are associated with LV hypertrophy                                                                                                                                                           |                    | 40         |
| CRP                                                                                  | Associated with AS severity (CRP is an independent predictor of severe AS (OR: 3.51, $P = .015$ ))                                                                                                                 | –                  | 41         |
| MMP12, C1QTNF1. and GDF15                                                            | Associated with AS severity                                                                                                                                                                                        | –                  | 42         |

Continued

Table 1 Continued

| Biomarker(s)                                                  | Main findings                                                                                                                                                              | Optimal cut-points                  | References |
|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|------------|
| Progression                                                   |                                                                                                                                                                            |                                     |            |
| LysoPA                                                        | Faster AS haemodynamic progression rate                                                                                                                                    | –                                   | 35         |
| Lp(a)                                                         | Faster AS progression rate and need for AVR                                                                                                                                | –                                   | 43–46      |
| Lp(a) and CRP                                                 | AS haemodynamic progression rate is observed in patients with both high Lp(a) and CRP (>2 mg/dL) levels, but the effect of Lp(a) is only modestly influenced by CRP levels | Lp(a) > 50 mg/dL<br>CRP > 2 mg/dL   | 17         |
| CRP                                                           | Faster AS haemodynamic progression rate                                                                                                                                    | CRP > 3 mg/dL                       | 41,47      |
| Lp-PLA2                                                       | Positive correlation between its activity and a faster progression rate of mild AS in patients                                                                             | Lp-PLA <sub>2</sub> Activity > 11.4 | 48         |
| Apo-CIII-Lp(a) complexes with Lp(a), OxPL-ApoB or OxPL-Apo(a) | Associated with faster progression rate in patients with mild to moderate AS                                                                                               | –                                   | 45         |
| Small and dense LDL particles                                 | Associated with faster progression of AS                                                                                                                                   | –                                   | 49         |
| ACE and AngII                                                 | Associated with faster progression of AS                                                                                                                                   | –                                   | 50,51      |
| DPP-4                                                         | DPP-4 inhibitors slow the progression rate of AS                                                                                                                           | –                                   | 52         |
| MMP12                                                         | Associated with faster progression of AS                                                                                                                                   | –                                   | 42         |

ACE, angiotensin-converting enzyme; AngII, angiotensin II; Apo-CIII-Lp(a), apolipoprotein-CIII-lipoprotein(a); AS, aortic stenosis; AV, aortic valve; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; Hs cTnI, high-sensitivity cardiac troponin I; Hs cTnT, high-sensitivity cardiac troponin T; Lp(a), lipoprotein(a); Lp-PLA2, lipoprotein-associated phospholipase A2; MMP12, matrix metalloproteinase-12; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCSK9, proprotein convertase subtilisin/kexin type 9; sST2, soluble suppression of tumorigenicity 2.

A heightened proportion of circulating small and dense LDL particles has been associated with an accelerated progression of AS.<sup>49</sup> Unfortunately, multiple randomized controlled trials have consistently demonstrated that statins do not influence the progression of AS, highlighting key differences between the initiation and propagation phases of the disease.

Other studies reported higher CRP serum levels in rapid AS progressors,<sup>41,47</sup> while data from the ASTRONOMER trial indicated that the fastest AS haemodynamic progression rate was observed in patients with both high Lp(a) (>50 mg/dL) and CRP (>2 mg/dL) levels, but the effect of Lp(a) was only modestly influenced by CRP levels.<sup>17</sup>

The lipoprotein-associated phospholipase A2 (Lp-PLA2) plays a role in the mineralization process and is highly expressed in stenotic aortic valves. It utilizes ox-LDLs and ox-PLs as substrates and generates free fatty acids and lysophosphatidylcholine, which exhibit pro-inflammatory and pro-calcifying properties.<sup>66</sup> A recent study demonstrated a positive correlation between elevated Lp-PLA2 activity and a faster progression rate of the disease in patients with mild AS.<sup>48</sup> This suggests that measuring Lp-PLA2 activity could be beneficial in predicting AS progression in patients at the early stages of the disease.

In patients operated on for severe symptomatic AS, higher circulating levels of angiotensin II (Ang II) were associated with inflammation and tissue remodelling within the explanted aortic valve.<sup>67</sup> Additionally, higher circulating levels of angiotensin-converting enzyme (ACE) and Ang II were associated with faster AS progression. Retrospective non-randomized studies reported Ang II receptor blockers, but not ACE inhibitors, are associated with less fibro-calcific process of aortic valve leaflets, especially in women,<sup>68</sup> and slower progression of AS.<sup>50,51</sup>

In the context of endothelial dysfunction, dipeptidyl peptidase-4 (DPP-4) secretion induces osteogenic differentiation. In a retrospective

study and animal study of AS, DPP-4 inhibitors have been shown to slow the progression rate of AS.<sup>52</sup> Conversely, an exploratory study of 248 patients did not demonstrate the protective effect of evogliptin, a DPP-4 inhibitor, on aortic valve calcification.<sup>69</sup>

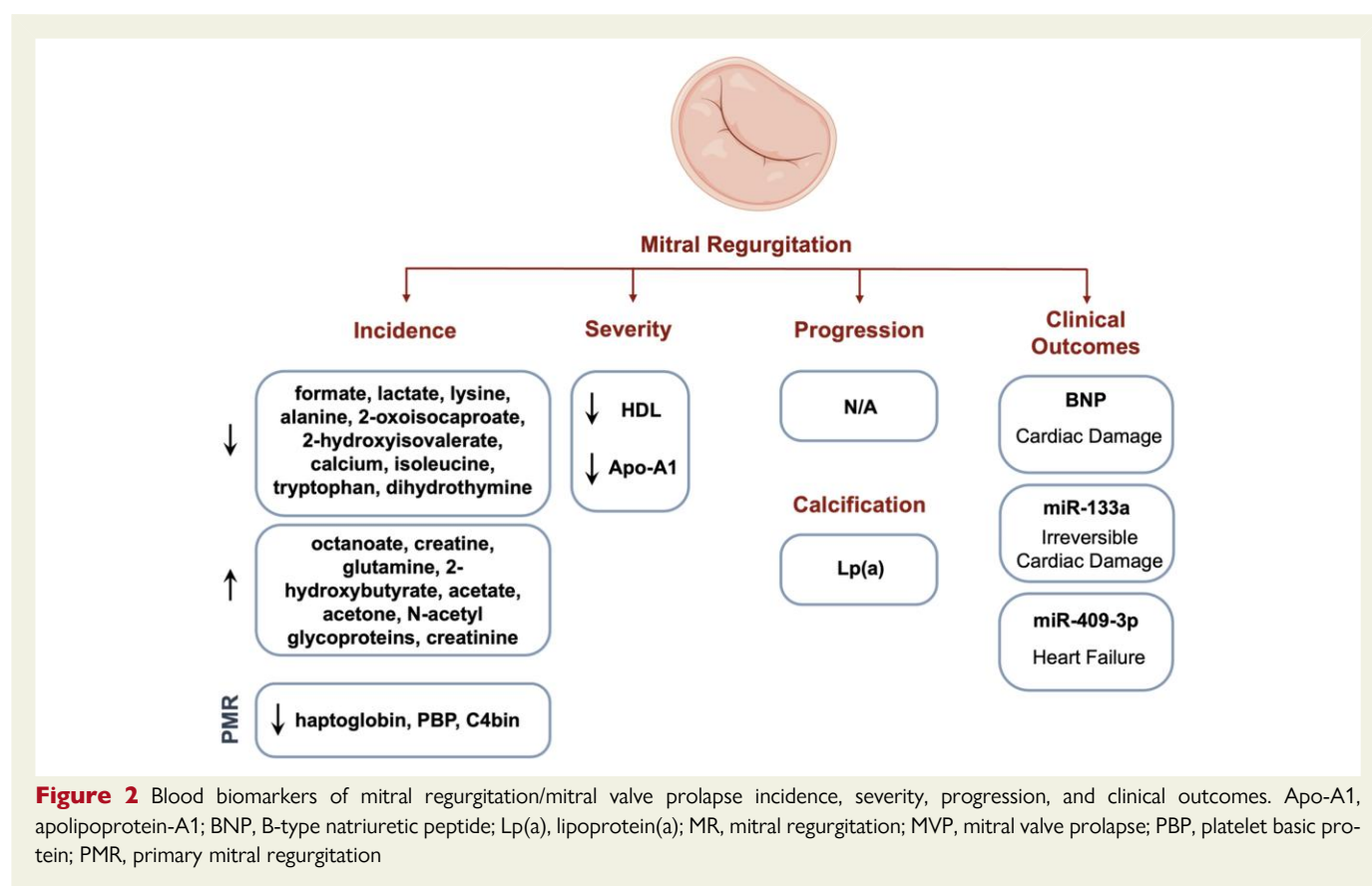
In a recent large-scale proteomic analysis, three extracellular matrix remodelling proteins [MMP12, C1QTNF1, and growth differentiation factor 15 (GDF-15)] were significantly associated with the presence of moderate or severe AS and MMP12 showed a strong association with AS haemodynamic progression.<sup>42</sup>

Studies have demonstrated that vitamin K antagonist (VKA) treatment is linked to dysregulation of the  $\gamma$ -carboxylation of matrix-Gla proteins (MGPs), which is protective of ectopic and thus valvular calcification.<sup>70</sup> In the future, monitoring biomarkers, and especially the changes in the ratio of carboxylated (active) to uncarboxylated (inactive) forms of MGP may be interesting to assess and predict the risk of aortic valve calcifications during VKA treatment.

Finally, several randomized clinical trials are currently ongoing to explore whether therapies can slow down or halt the progression of AS: niacin (EAVaLL, NCT02109614), PCSK9 inhibitors (NCT03051360), Lp(a) lowering using pelacarsen [Lp(a)FRONTIERS CAVS, NCT05646381], renin–angiotensin–aldosterone system inhibitors (ARBAS, NCT04913870), or DPP-4 inhibitors (EVOID-AS, NCT05143177).

Aortic regurgitation

Aortic regurgitation (AR), especially after transcatheter AVR (TAVR), has been associated with lower levels of high-molecular-weight multimers of vWF. Indeed, turbulent flow induced by AR provokes an excessive cleavage of the high-molecular-weight multimers of vWF. Turbulent flow occurs also in mitral regurgitation (MR) and AS,



especially when severe.<sup>71</sup> Recent data have emphasized the value of<sup>63</sup> a point-of-care measure of vWF factor-dependent platelet function [closure time (CT) adenosine diphosphate (ADP)]. Perturbation of vWF affects haemostasis, which can be evaluated with CT-ADP. However, except in a defined clinical setting, such as transcatheter intervention (aortic or mitral valve), the use of vWF or CT-ADP may be limited to assess the severity of AR and other VHD.

## Mitral regurgitation

The exploration of the metabolic profile associated with MR revealed a decreased level of formate, lactate, lysine, alanine, 2-oxoisocaproate, 2-hydroxyisovalerate, calcium, isoleucine, tryptophan, and dihydrothymine, along with an increased level of octanoate, creatine, glutamine, 2-hydroxybutyrate, acetate, acetone, N-acetyl glycoproteins, and creatinine.<sup>72</sup> Recent studies have demonstrated lower plasma levels of haptoglobin, platelet basic protein (PBP), and complement component C4b in patients with degenerative MR.<sup>73,74</sup> Haemolysis and platelet dysfunction may be related to the disease, probably as markers of increased shear stress. Lower plasma levels of HDL and Apo-A1 were also associated with MR severity.<sup>73</sup> However, despite being of great scientific interest, microRNAs, proteomic and metabolic profiles are not yet ready to be used in clinical routine to identify mitral valve prolapse, the severity of the disease, or its evolution. The mitral valve shares a similar pathological process with the aortic valve, leading to stenosis; however, limited data are available regarding its relationship with Lp(a). While one study found an association with mitral stenosis, another found it only with mitral calcification.<sup>75,76</sup> Interestingly, Lp(a) was linked to the onset of mitral valve calcification but not its

progression, mirroring findings for aortic valve calcification in that particular study.<sup>77</sup> B-type natriuretic peptide activation in MR reflects primarily the ventricular and atrial overload consequences rather than the degree of MR, however, higher BNP level independently predicts adverse events.<sup>78–81</sup> An overview of blood biomarkers of MR and mitral valve prolapse incidence, severity, progression, and clinical outcomes is provided in [Figure 2](#) and [Table 2](#).

## Biomarkers associated with cardiac damage in valve disease

### Aortic stenosis

#### Natriuretic peptides (B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, and their ratios)

An overview of blood biomarkers of cardiac damage in AS is provided in [Figure 3](#). B-type natriuretic peptide and NT-proBNP have been extensively validated in AS,<sup>28,29</sup> but also in atrial fibrillation, heart failure, and mortality before or after intervention.<sup>4,89–91</sup> Unfortunately, both BNP and NT-proBNP levels increase with age, are different between men and women, and dependent on the assay used (especially for BNP).<sup>92,93</sup> Thus, thresholds to define impaired left ventricular function vary from one study to another. The concept of 'clinical activation' or natriuretic peptide ratio, which is the ratio of the measured to the maximal normal value of the natriuretic peptide for the age and sex of the patient and for the used assay, has been proposed to overcome these sex/age/assay variabilities. A BNP ratio >2 or 3 appears to have an

**Table 2** Blood biomarkers associated with presence, severity, progression and outcomes in other native valvular heart diseases

| Biomarker(s)                            | Main findings                                                                                                                                                                                                                                                                                                            | Optimal cut-points | References |
|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------|
| Mitral regurgitation                    |                                                                                                                                                                                                                                                                                                                          |                    |            |
| Metabolic profile                       | A decrease level of formate, lactate, lysine, alanine, 2-oxoisocaproate, 2-hydroxyisovalerate, calcium, isoleucine, tryptophan, and dihydrothymine, and an increased level of octanoate, creatine, glutamine, 2-hydroxybutyrate, acetate, acetone, <i>N</i> -acetyl glycoproteins, and creatinine are associated with MR | —                  | 72         |
| Haptoglobin, PBP, C4b                   | Lower levels are observed in patients with degenerative MR                                                                                                                                                                                                                                                               | —                  | 73,74      |
| HDL and Apo-A1                          | Lower levels are associated with MR severity                                                                                                                                                                                                                                                                             | —                  | 73         |
| Lp(a)                                   | Elevated levels are associated with mitral and aortic valve calcification and aortic valve stenosis                                                                                                                                                                                                                      | —                  | 76,77      |
|                                         | Lp(a) was associated with the onset of mitral valve calcification but not its progression over time                                                                                                                                                                                                                      | —                  | 77         |
| BNP                                     | BNP ratio < 1 in asymptomatic patients is associated with good prognosis, even in severe MR                                                                                                                                                                                                                              | —                  | 81,82      |
|                                         | Serial BNP measurements are proposed to detect onset of LV impairment and trigger intervention                                                                                                                                                                                                                           | —                  | 83         |
|                                         | BNP levels are associated with myocardial health rather than MR severity and are associated with mortality and heart failure                                                                                                                                                                                             | —                  | 78         |
| miRNAs                                  | miR-409–3p could be a biomarker of heart failure                                                                                                                                                                                                                                                                         | —                  | 85         |
|                                         | miR-133a might indicate irreversible myocardial damage                                                                                                                                                                                                                                                                   | —                  | 86         |
| Aortic regurgitation                    |                                                                                                                                                                                                                                                                                                                          |                    |            |
| High-molecular-weight multimers of vWF  | Lower plasma levels are associated with the presence of aortic regurgitation                                                                                                                                                                                                                                             | —                  | 71         |
| Hs cTnT and red cell distribution width | Association between hs-TnT [OR (95% CI): 1.38 (1.08–1.69); <i>P</i> = .02] and RDW [OR (95% CI): 1.53 (1.01–2.33); <i>P</i> = .03] in predicting post-operative major complications including death in patients with severe symptomatic AR undergoing aortic valve surgery                                               | —                  | 87         |
| BNP                                     | In asymptomatic AR, BNP may play an important role in assessing subclinical deterioration and predicting worse clinical outcomes                                                                                                                                                                                         | —                  | 88         |

ANP, atrial natriuretic peptide; Apo-A1, apolipoprotein A1; AR, aortic regurgitation; BNP, B-type natriuretic peptide; hs cTnT, high-sensitivity cardiac troponin T; Lp(a), lipoprotein(a); LV, left ventricle; PBP, platelet basic protein; RDW, red cell distribution width; vWF, von Willebrand factor.

important impact on mortality.<sup>4</sup> Therefore, a BNP ratio >3 has been proposed as a Class IIa recommendation for AVR in low-risk patients with asymptomatic AS in the current European and American guidelines for the management of patients with VHD.<sup>2,3</sup>

### High-sensitivity troponins

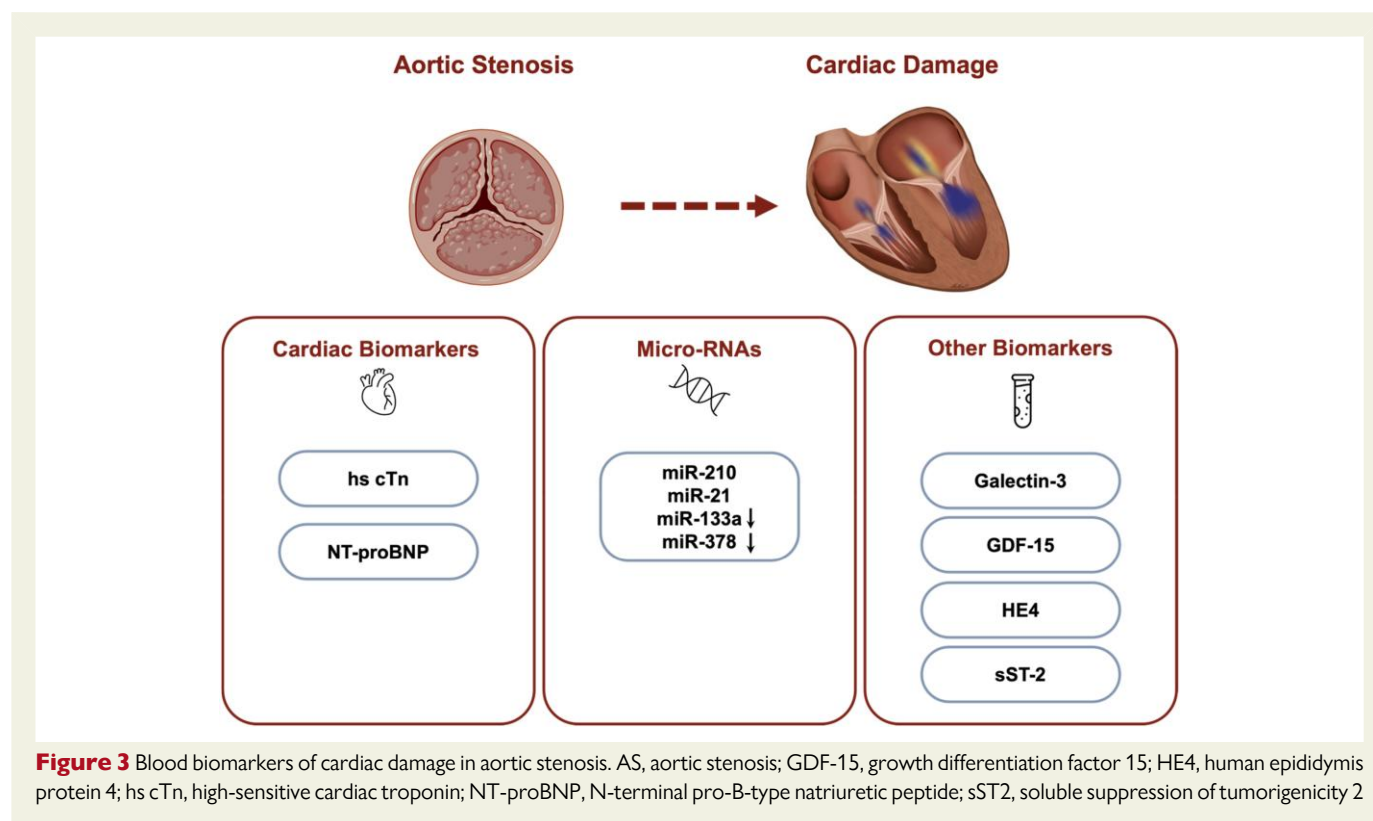
The second most common blood biomarkers in VHD are the cardiac troponins (cTn). Cardiac troponins are widely used to diagnose myocardial infarction as it is secreted in the bloodstream from the myocyte cytosolic pool after cardiac injury. The development of high-sensitivity (hs) assay allows measurement of lower levels of troponins and therefore, detection of early myocardial injury associated with VHDs before the development of overt myocardial dysfunction. In AS populations, hs cardiac troponin I (cTnI) is associated with the degree of left ventricular hypertrophy and myocardial fibrosis rather than the severity of associated coronary artery disease.<sup>6,31</sup> Cardiac troponin I (cTnI) was used

as a screening tool to detect subclinical left ventricular decompensation in the EVOLVED randomized controlled trial, in order to help optimize the timing of aortic valve intervention.<sup>94</sup> In the future, elevated hs cTnI could be used to identify patients with asymptomatic severe AS who should be referred to early AVR.

### Other biomarkers

Several biomarkers related to cardiovascular stress and myocardial fibrosis (sST2, GDF-15, and galectin 3) and micro-RNA related to cardiac remodelling and injury (miR-210, miR-21, miR-133, miR-22, miR-486, miR-204, etc.) have been associated with VHDs severity, symptoms and/or outcomes.<sup>36–40</sup>

In several small AS studies, elevated plasma levels of these biomarkers have been associated with symptom status, AS severity, several parameters of cardiac remodelling, and outcomes.<sup>32,59,95–98</sup> The human epididymis protein 4 (HE4) is a four-disulfide core domain 2 (WFDC2)



acidic protein that is known as a protease inhibitor that suppresses the activities of multiple proteases, such as serine proteases and matrix metalloproteinases.<sup>99–101</sup> This is a promising blood biomarker which has been associated with renal and cardiac fibrosis, increased rates of heart failure, and cardiac events.<sup>102–104</sup> In recent studies including patients with severe AS, higher levels of HE4 prior to TAVR were associated with diffuse myocardial fibrosis and increased rates of adverse events following the procedure.<sup>105</sup>

In AS, lower miR-378 has been associated with more advanced left ventricular hypertrophy,<sup>40</sup> miR-21 with left ventricular fibrosis,<sup>36</sup> miR-210 with mortality<sup>39</sup>, and miR-133a has been found to be a predictor of regression of left ventricular hypertrophy after surgical AVR (SAVR).<sup>106</sup>

## Mitral regurgitation

Overall, very few studies have been performed to assess myocardial damage in other VHDs. In MR, these new biomarkers are even less studied, and results are conflicting.<sup>107,108</sup> In primary MR, the BNP ratio could be used to trigger intervention in asymptomatic patients. Interestingly, the impact of BNP ratio appears to be blunted after early intervention, underlining the possibility of reversibility of cardiac damage.<sup>81</sup> Moreover, a BNP ratio <1 in asymptomatic patients is correlated with good prognosis under medical management, even in severe MR.<sup>81,82</sup> Serial BNP measurements have also been proposed to detect onset of left ventricular impairment and trigger intervention,<sup>83</sup> keeping in mind the natural variation of natriuretic peptide levels.<sup>109</sup> In MR patients, miR-409-3p, one of the most potent fibrinogen downregulating miRs while decreasing fibrinogen production, could be a biomarker of heart failure incidence,<sup>85</sup> and miR-133a might indicate irreversible myocardial damage.<sup>86</sup>

## Biomarkers associated with clinical outcomes before and after intervention

Several blood biomarkers can provide a readout that associates with clinical outcomes in patients with advanced VHD both before and after valve intervention. It is important to highlight that the presence of symptoms remains the primary criterion for considering intervention in VHD. However, this criterion is subjective and often influenced by multiple factors, which may explain why a substantial proportion of patients—around one-third in case of severe AS—experience no improvement in symptoms or functional capacity following intervention.<sup>110,111</sup> In this context, blood biomarkers could play a crucial role in providing accurate and objective insights into the impact of VHD and may serve as a valuable tool in the decision-making process. An overview of blood biomarkers associated with clinical outcomes, before and after intervention is provided in [Table 3](#).

## Aortic stenosis

### Prior to aortic valve replacement

Any biomarker that identifies patients who transition more rapidly towards severe AS and thus the need for AVR would be of clinical value. As discussed, elevated Lp(a) are consistently associated with more rapid disease progression, and this translates into patients requiring AVR than those with normal levels. A recent proteomic analysis identified interleukin-6 (IL-6) and fibroblast growth factor 23 (FGF-23) as strong predictors of adverse outcomes in AS.<sup>116</sup> miRNA-21 was associated with mortality in patients with AS.<sup>36</sup> Recently, miRNA-101-3p was found in the myocardium of patients with AS which correlated with

**Table 3** Blood biomarkers associated with outcomes in aortic stenosis

| Biomarker(s)                                | Main findings                                                                                                                                                                                       | Optimal cut-points | References |
|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|------------|
| Hs cTnT                                     | Higher plasma levels are associated with all-cause mortality [HR (95% CI): 18.0 (2.4–136.4)]                                                                                                        | >.027 g/L          | 112–114    |
| Hs cTnI                                     | Higher plasma levels are associated with AVR or cardiovascular death [HR (95% CI): 1.77 (1.22–2.55), <i>P</i> = .002]                                                                               | –                  | 6          |
| HE4                                         | Higher serum levels of HE4 are associated with higher rates of treatment futility, rehospitalization for heart failure, and all-cause mortality                                                     | ≥130 pmol/L        | 84         |
| miRNAs                                      | miR-133 predictor of regression of LV hypertrophy after SAVR                                                                                                                                        |                    | 106        |
| IL-6 and FGF-23                             | Predict heart failure hospitalization (using machine-learning multimarker models)                                                                                                                   | –                  | 115        |
| sST2                                        | Higher plasma levels are associated with long-term mortality (following both SAVR and TAVR)                                                                                                         | –                  | 7,116–118  |
| BNP                                         | Higher plasma levels are associated with long-term mortality (following both SAVR and TAVR)                                                                                                         | –                  | 4,89,119   |
| NT-proBNP                                   | Higher plasma levels are associated with long-term mortality (following both SAVR and TAVR)                                                                                                         | –                  | 4,89,119   |
| CA-125                                      | Higher plasma levels are associated with increased risk of adverse events following TAVR [HR (95% CI): 2.18 (1.11–4.26); <i>P</i> = .023] and MACE [HR (95% CI): 1.77 (1.05–2.98); <i>P</i> = .031] | –                  | 120        |
| GDF-11                                      | Higher plasma levels are associated with post-op complications and re-hospitalizations after AVR                                                                                                    | –                  | 121        |
| GDF-15                                      | Higher plasma levels are associated with poor prognosis after TAVR                                                                                                                                  | –                  | 95,122     |
| Hypoalbuminaemia                            | Lower serum levels are associated with increased mortality after TAVR ( <i>P</i> < .001)                                                                                                            | <3.5 g/dL          | 123        |
| High-molecular-weight multimers vWF ratio   | Reduced ratio is associated with increased mortality at 1-year post-intervention                                                                                                                    | <.8                | 62,124,125 |
| CT-ADP                                      | Increased CT-ADP is associated with increased mortality at 1-year post-intervention                                                                                                                 | ≥180 s             | 62         |
| Red blood cell distribution width expansion | Baseline RDW is independently associated with all-cause mortality after TAVR [adjusted HR (95% CI): 2.70 (1.40–5.22), <i>P</i> = .003]                                                              | ≥15.5%             | 126        |

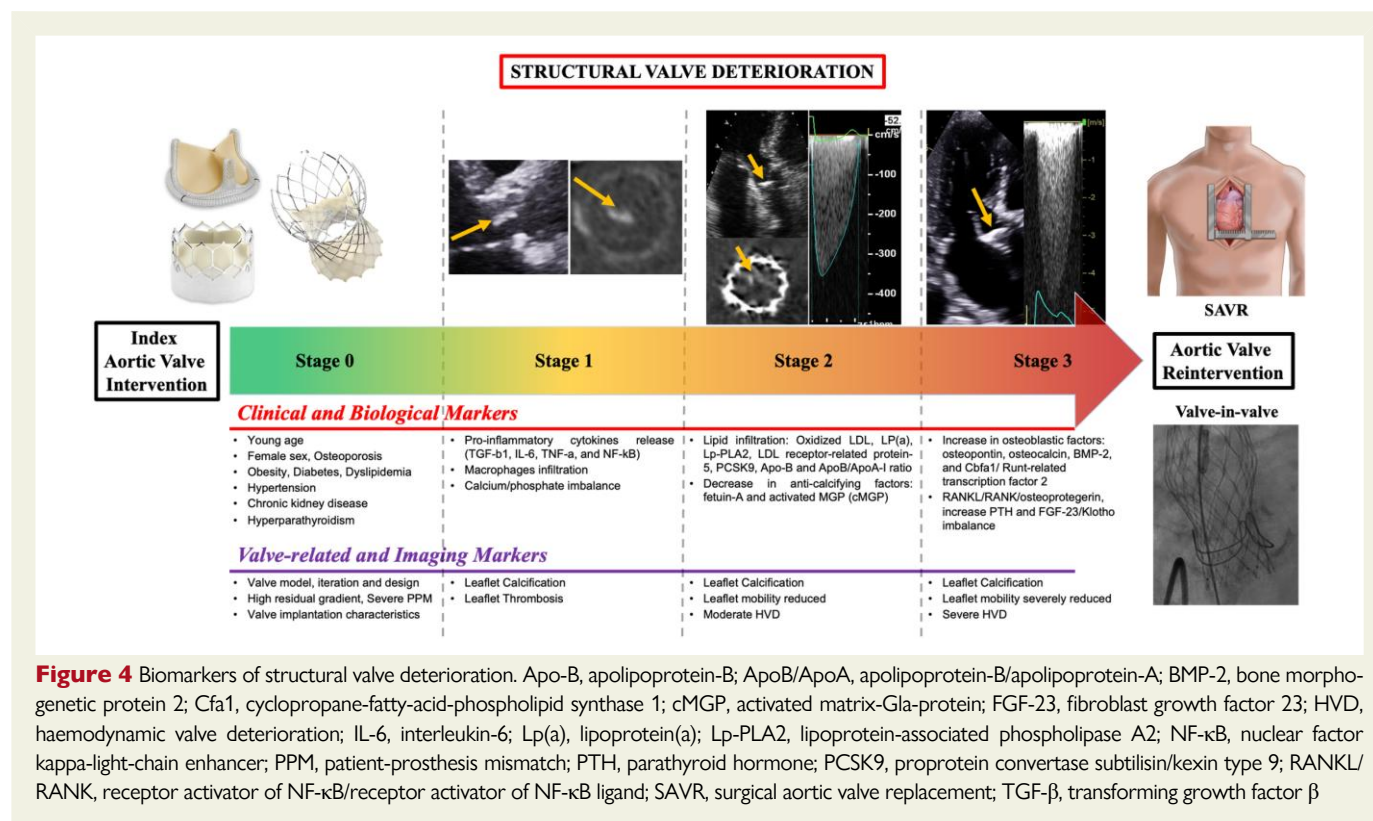
ACE, angiotensin-converting enzyme; AngII, angiotensin II; Apo-CIII-Lp(a), apolipoprotein CIII-lipoprotein(a); AS, aortic stenosis; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; CA-125, cancer antigen 125; CRP, C-reactive protein; CT-ADP, closure time with adenosine diphosphate; DPP-4, dipeptidyl peptidase-4; FGF-23, fibroblast growth factor 23; GDF-11, growth differentiation factor 11; GDF-15, growth differentiation factor 15; HE4, human epididymis protein 4; Hs cTnI, high-sensitivity cardiac troponin I; Hs cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; Lp(a), lipoprotein(a); Lp-PLA2, lipoprotein-associated phospholipase A2; LV, left ventricle; MMP12, matrix metalloproteinase-12; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCSK9, proprotein convertase subtilisin/kexin type 9; sST2, soluble suppression of tumorigenicity 2; TAVI, transcatheter aortic valve implantation; vWF, von Willebrand factor.

increased preoperative valvulo-arterial impedance, Ang II receptor, ACE, and left ventricular mass regression after surgery.<sup>127</sup> A recent study including patients with low-flow, low-gradient AS reported an incremental value of hs cTnT in adjunction to BNP for predicting increased risk of mortality.<sup>127</sup>

**After aortic valve replacement**

Post-AVR, once the valve has been replaced, events are more closely related to myocardial health and left ventricular decompensation. Endpoints such as heart failure, AS-related hospital admissions, cardiovascular death, and death are of particular importance. Consistent studies have demonstrated that elevated plasma levels of BNP and NT-proBNP are associated with adverse outcomes, including long-term mortality, following both SAVR and TAVR.<sup>4,89,119</sup> Elevated plasma levels of cTnI are also associated with post-AVR outcomes including cardiovascular and all-cause death,<sup>6</sup> and hs cTnT levels are associated with worse outcomes after

intervention for severe AS<sup>128</sup> and severe AR.<sup>87</sup> Carbohydrate antigen 125 (CA-125) is a glycoprotein that is secreted by mesothelial cells in the context of tissue inflammation and injury. Elevated plasma levels of CA-125 are associated with symptoms, an increased risk of adverse clinical events following TAVR, and have demonstrated incremental value over BNP, the logistic EuroSCORE, and New York Heart Association functional class.<sup>120</sup> Growth differentiation factor 11 is involved in the aging processes and may represent a marker of patients' frailty. Growth differentiation factor 11 has been found to be a predictor of post-operative complications and re-hospitalizations after AVR.<sup>121</sup> Growth differentiation factor 15 is increased in patients with AS and appears to be a soluble correlate of patients' frailty, independent of indices of left ventricular dysfunction.<sup>129</sup> sST2 has been found to be a powerful predictor of all-cause mortality following TAVR and SAVR. Hypoalbuminaemia, a well-known indicator of frailty, has been associated with poor prognosis after TAVR and could thus be useful for risk stratification prior to AVR.<sup>123</sup> Following AVR, vWF inactivation is also observed in cases of significant PVL or



prosthesis–patient mismatch causing highly turbulent flow.<sup>62,124</sup> A recent study showed that the ratio of high-molecular-weight multimers of vWF normalized after TAVR in patients without residual PVL but did not normalize or partially normalize when post-implantation PVL was present.<sup>62,125</sup> This study also showed that a reduced ratio of high-molecular-weight multimers of vWF was associated with increased mortality at 1-year post-intervention. While these data suggest that vWF could be useful post-AVR to biologically detect the presence of high shear stress phenomena such as PVL, 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 elucidated. Red blood cell distribution width expansion, associated with inflammation, renal dysfunction, and atherosclerosis, is also associated with increased mortality after TAVR.<sup>126</sup>

## Mitral regurgitation

Blood biomarkers have also demonstrated an association with clinical outcomes in other forms of VHD. Again, BNP and NT-proBNP are the most widely studied. In patients with primary MR, BNP levels are also associated with markers of cardiac damage rather than the severity of the valve lesion and provide a strong prediction of future cardiovascular events, in particular death and heart failure.<sup>78</sup>

## Biomarkers associated structural valve deterioration, valve thrombosis, and paravalvular leak

### Structural valve deterioration

Over the past two decades, the number of bioprosthetic valve implantations, either surgically or percutaneously, has drastically

increased.<sup>130</sup> This rise is largely due to the expansion of TAVR, whose indications have been extended to lower risk and/or younger patients, as well as the preference for biological over mechanical valves, driven by the advantages of avoiding long-term anticoagulation. Despite important advances in valve design and both transcatheter and surgical procedures, bioprosthetic valves are still prone to SVD and responsible for significant morbidity, mortality, and valve re-intervention during follow-up. Early detection of SVD is thus crucial to avoid irreversible cardiac damages and adverse clinical outcomes. Clinical, biological, and imaging biomarkers can help in identifying patients at risk for early SVD-related haemodynamic dysfunction, allowing individualized primary prevention and follow-up strategies, and also in helping to anticipate bioprosthetic valve failure and plan for valve re-intervention procedures (Figure 4).

Clinical and biological markers associated with SVD are summarized in Table 4. Younger age is debated because studies' endpoints were re-intervention which is more often considered in young vs old patients for the same degree of SVD. Imaging-based studies did not confirm this association.<sup>131</sup> Intriguingly, female sex was found to be associated with SVD.<sup>132</sup> This finding could be related to the phospho-calcic metabolism dysregulation associated with menopause and osteoporosis, such as observed in hyperparathyroidism or chronic kidney disease. Several pathways were identified as SVD promoters by activating pro-calcific mechanisms in the bioprosthetic valve tissues: matrix-GLA-protein, fetuin-A, osteoprotegerin/RANK/RANKL, and fibroblast growth factor-23/Klotho axis.<sup>133</sup> Interestingly, VKAs may also promote SVD through blockage of the matrix-GLA-protein pathway.<sup>134</sup> Obesity and metabolic disorders affect one-third of patients implanted with a bioprosthesis and are strongly associated with early SVD, especially metabolic syndrome, dyslipidemia, and diabetes (HOMA index)<sup>135–137</sup> by inducing endothelial dysfunction, oxidative stress, local and systemic inflammation (LT, macrophages, transforming

**Table 4** Blood biomarkers associated with structural valve deterioration, paravalvular leak, thrombosis and adverse events in prosthetic valves

|                                                                                    | Main findings                                                                                                                                                                                                                               | Optimal cut-points                                             | References |
|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|------------|
| <b>SVD</b>                                                                         |                                                                                                                                                                                                                                             |                                                                |            |
| PCSK9                                                                              | High plasma levels of PCSK9 are associated with bioprosthetic SVD                                                                                                                                                                           | >305 ng/mL                                                     | 137–140    |
| Oxidized-LDLs/HDL ratio                                                            | High plasma levels of oxidized-LDL/HDL ratio are associated with bioprosthetic SVD                                                                                                                                                          | ≥25.4 U/L                                                      | 137–140    |
| Apo-B                                                                              | High plasma levels of Apo-B and ApoB/ApoA-I ratio are associated with bioprosthetic SVD                                                                                                                                                     | —                                                              | 137–140    |
| ApoB/ApoA-1 ratio                                                                  | High plasma levels of ApoB/ApoA-I ratio are associated with bioprosthetic SVD                                                                                                                                                               | —                                                              | 137–140    |
| Total cholesterol and triglycerides                                                | High plasma levels of total cholesterol and triglycerides are associated with re-intervention for valve failure in young patients (<57 years)                                                                                               | Total cholesterol level >240 mg/dL or triglycerides >123 mg/dL | 132        |
| sCD14                                                                              | High plasma levels of sCD14 are associated with bioprosthetic SVD                                                                                                                                                                           | —                                                              | 141        |
| Calcium-phosphorus product                                                         | Higher calcium-phosphorus product is a strong predictor of bioprosthesis calcification                                                                                                                                                      | —                                                              | 142        |
| <b>Thrombosis</b>                                                                  |                                                                                                                                                                                                                                             |                                                                |            |
| IgM and IgG anticardiolipin antibodies                                             | Higher plasma levels may result in thrombosis in mitral, aortic and tricuspid prosthetic valve                                                                                                                                              | —                                                              | 143        |
| Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and CRP                     | Higher plasma levels are potential inflammatory biomarkers of mitral thrombosis                                                                                                                                                             | —                                                              | 144        |
| <b>PVL</b>                                                                         |                                                                                                                                                                                                                                             |                                                                |            |
| High-molecular-weight multimers of vWF                                             | Lower plasma levels are associated with the presence of paravalvular leaks                                                                                                                                                                  | —                                                              | 62         |
| CT-ADP                                                                             | Higher CT-ADP is associated with the presence of paravalvular leaks                                                                                                                                                                         | —                                                              | 145        |
| <b>Outcomes</b>                                                                    |                                                                                                                                                                                                                                             |                                                                |            |
| NT-proBNP, haemoglobin, reticulocyte production, LDH, haptoglobin and schistocytes | Associated with the risk of developing heart failure and severe haemolysis                                                                                                                                                                  | —                                                              | 146,147    |
| High-molecular-weight multimers of vWF                                             | Lower plasma levels are associated with increased mortality at 1 year following TAVR [adjusted HR (95% CI): 3.24 (1.58–6.63), $P = .001$ ]                                                                                                  | <.8                                                            | 62         |
| CT-ADP                                                                             | Higher CT-ADP is associated with an increased rate of late major/ life-threatening bleeding complications [adjusted HR (95% CI): 3.08 (1.62–5.81), $P = .0005$ ] and 1-year mortality [adjusted HR (95% CI): 3.86 (1.91–7.75), $P < .001$ ] | ≥180 s                                                         | 62,145     |

Apo-B, apolipoprotein-B; ApoB/ApoA-1, apolipoprotein B/apolipoprotein A-1 ratio; CRP, C-reactive protein; CT-ADP, closure time with adenosine diphosphate; IgG, immunoglobulin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; NT-proBNP, N-terminal proB-type natriuretic peptide; PCSK9, proprotein convertase subtilisin/kexin type 9; PVL, paravalvular leak; sCD14, soluble cluster of differentiation 14; SVD, structural valve deterioration; vWF, von Willebrand factor.

growth factor beta-1 protein, IL-6, TNF- $\alpha$  and NF- $\kappa$ B) and lipid infiltration (LDL, Lp(a), Lp-PLA2 and PCSK9). High plasma level of PCSK9 (>305 ng/mL), oxidized-LDLs/HDL ratio (≥25.4 U/L), Apo-B and ApoB/ApoA-I ratio are predictors of bioprosthetic SVD.<sup>137–139</sup> In patients younger than 57 years, total cholesterol >240 mg/dL or triglycerides >123 mg/dL were demonstrated to be two predictors of re-intervention for valve failure.<sup>132</sup>

Smoking increases oxidative stress and thus promotes the early onset of SVD.<sup>140</sup> CD14, a membrane glycoprotein present at the surface of monocytes and macrophages, can be secreted by these cells or the liver, and the soluble form of CD14 (sCD14) has been related to SVD.<sup>141</sup> Finally, a higher calcium-phosphorus product is a strong predictor of bioprosthesis calcification and patients with lower preoperative creatinine clearance (<30 mL/min) are at higher risk of ≥Stage 2 SVD.<sup>142</sup>

## Valve thrombosis

Clinical prosthetic valve thrombosis is a rare but serious complication of valve replacement, most often encountered with mechanical prostheses. Thrombosis of a bioprosthetic valve is usually diagnosed in the early post-operative period, when endothelialization of the suture zone is not yet complete. The significant morbidity and mortality associated with this condition warrants rapid diagnostic evaluation. In valve thrombosis, biological tests typically show slightly modified inflammatory markers and/or a subtherapeutic anticoagulation profile (international normalized ratio, specific anti-Xa activity). D-dimer, which detects the presence of cross-linked fibrin degradation products, has been demonstrated to be a useful marker of coagulation activation and may consequently be raised in patients with thrombosis of a bioprosthetic valve. IgM and IgG anticardiolipin antibodies may result in a tendency to thrombosis in mitral, aortic, and tricuspid prosthetic valves and could be considered in all these patients.<sup>143</sup> Increased neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and CRP are potential inflammatory biomarkers of mitral thrombosis.<sup>144</sup>

## Paravalvular leak

Circulating biomarkers may also help to identify patients with significant residual PVL who may benefit from additional valve intervention. von Willebrand factor is implicated in platelet adhesion and aggregation at sites of vascular injury. After TAVR, high-molecular-weight multimers of vWF ratio may help to detect significant residual aortic PVL.<sup>62</sup> Additionally, recent data have emphasized the value of a point-of-care measure of vWF-dependent platelet function (CT ADP) in the monitoring of immediate PVL. A post-procedural CT-ADP lower than 180 s is a predictor of significant PVL following TAVR and may independently contribute to major/life-threatening bleedings.<sup>145</sup> These data should still be confirmed in larger patient cohorts from independent centres to ensure their reliability and generalizability. Of note, the PFA-100 data do not accurately reflect overall platelet reactivity, and since the results might be influenced by medication, low platelet count, haematocrit and levels of vWF antigen, the specificity of this technology remains a major limitation.

In patients with chronic PVL, monitoring NT-proBNP, haemoglobin, reticulocyte production, lactate dehydrogenase, haptoglobin and examination for schistocytes is important to determine the risk of developing heart failure and severe haemolysis, which would argue for further intervention.<sup>146,147</sup>

## Future perspectives

Multimic approaches to biomarker discovery led to the emergence of several new potentially promising biomarkers. Some biomarkers, particularly those from recent metabolomic studies and miRNAs or long-coding RNAs, still need to be validated in large and diverse clinical cohorts. Thus, additional data on novel biomarkers are still needed. In addition, as described in heart failure therapy, biomarkers could be used to identify the optimal timing for intervention, stratify risk, and assess the response to both interventional and pharmaceutical therapies. One could hope that with specific biomarkers, disease progression, myocardial impairment, and post-intervention complications could be monitored in VHDs in the future.

Interestingly, all the presented biomarkers do not have the same triggers and power and thus, their levels are not perfectly correlated. The association of their evaluation could then be synergistic and complementary. The first interesting association is the co-evaluation of BNP and troponin. Indeed, elevation of both BNP and troponin appear to

add prognostic value when compared with only one elevated biomarker in patients with low-flow, low-gradient AS.<sup>148</sup> In a recent publication by Lindman *et al.*,<sup>149</sup> a new concept of cardiovascular stress multimarker approach in a population of asymptomatic and symptomatic patients undergoing SAVR has been studied. The biomarkers reflected diverse pathways such as myocyte injury, myocyte stress, inflammation, fibrosis, and neurohormonal activation. They found that an increasing number of elevated biomarkers forming a multimarker score, such as NT-proBNP, hs cTnT, HE4, sST2, CA-125, hs CRP, and GDF-15, were associated with higher mortality and higher rate of all-cause and cardiovascular hospitalization after SAVR. A similar multimarker approach has been also validated in patients with severe AS undergoing TAVR.<sup>105</sup> These findings suggest that a multimarker approach may be useful in the surveillance of asymptomatic patients with severe AS and may serve as a trigger for AVR even before symptoms occur and when natriuretic peptide levels are still low.

Finally, it should be emphasized that the number of studies exploring the association between biomarkers and tricuspid regurgitation is very limited and that individual blood biomarker specificity is still lacking in VHDs. This limitation underscores the need for combining multiple biomarkers to improve diagnostic accuracy and prognostic assessment. With a multimarker approach, it may be possible to capture a more comprehensive picture of the underlying disease processes, enhancing the precision of clinical decision-making.

## Conclusions

Several biomarkers that reflect differential pathological processes have been shown to have an incremental value over classic and echocardiographic criteria and clinical assessment for risk stratification in patients with VHD. Established blood biomarkers such as Lp(a), BNP, NT-proBNP, and hs troponin can be useful in assessing the severity and progression of VHD and the optimal timing for intervention. The plasma levels of Lp(a) or OxPL can be used to identify patients with AS who are at risk of fast stenosis progression and could be considered for Lp(a) lowering drugs in the future. An elevated BNP ratio or an increase in BNP or NT-proBNP during follow-up in the individual patient or an elevated hs cTnI may be used in the clinical setting to identify patients with asymptomatic severe AS who should be considered for early AVR.

However, there are major overlaps of the value ranges of these blood biomarkers between different groups of severity and prognosis, and further research will be necessary to determine the meaningful clinical thresholds for individual patients (i.e. men vs women).

Emerging biomarkers hold promise for risk stratification and individualized disease management. Contemporary data suggest that combining multiple biomarkers to develop a global score reflecting VHD activity at the level of the valve and the myocardium need to be confirmed. Ultimately, a multimarker approach may be useful to optimize the timing of surgery in patients with VHD or the occurrence of bioprosthetic valve failure after surgical or transcatheter valve replacement.

Additionally, the important lack of evidence and data on biomarkers in VHD of the mitral, tricuspid, pulmonary valves, and even on regurgitation of the aortic valve needs to be addressed in the future to help the management of the patients suffering from these diseases.

## Supplementary data

Supplementary data are not available at *European Heart Journal* online.

## Declarations

### Disclosure of Interest

A.C. is the proctor for Abbott Vascular and received speaker fees for Abbot Vascular, Edwards Lifescience, GE Healthcare, BMS, MSD, Pfizer. J.T. is a consultant for Abbott Structural, Edwards Lifesciences, General Electric, Philips and Pi-Cardia. R.T.H. reports speaker fees from Abbott Structural, Baylis Medical, Edwards Lifesciences, and Philips Healthcare; she has institutional consulting contracts for which she receives no direct compensation with Abbott Structural, Anteris, Boston Scientific, Edwards Lifesciences, Medtronic, Novartis, and Philips Healthcare; she is the Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored valve trials, for which she receives no direct industry compensation. M.-A.C. has received funding from Edwards Lifesciences, Medtronic, Pi-Cardia, Novartis and Rednvia for research studies and CT core laboratory analyses, for which she received no personal compensation. B.L. is a consultant for Edwards Lifesciences, Medtronic, Anteris, and Astra Zeneca, received investigator-initiated research funding from Edwards Lifesciences, and is PI of the biobanks for the EARLY TAVR and PROGRESS trials. P.P. has received funding from Edwards Lifesciences, Medtronic, Pi-Cardia, Cardiac Success, and Novartis for echocardiography core laboratory analyses and research studies in the field of valvular heart disease, for which he received no personal compensation. P.P. has received lecture fees from Edwards Lifesciences and Medtronic. The remaining authors have no conflicts of interest to declare.

### Data Availability

No data were generated or analysed for this manuscript.

### Funding

All authors declare no funding for this contribution.

## References

- Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**: 561–632. <https://doi.org/10.1093/eurheartj/ehab395>
- Writing Committee Members; Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2021;**77**:e25–197. <https://doi.org/10.1016/j.jacc.2020.11.018>
- Coisne A, Lancellotti P, Habib G, Garbi M, Dahl JS, Barbanti M, et al. ACC/AHA and ESC/EACTS guidelines for the management of valvular heart diseases: JACC guideline comparison. *J Am Coll Cardiol* 2023;**82**:721–34. <https://doi.org/10.1016/j.jacc.2023.05.061>
- Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, et al. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. *J Am Coll Cardiol* 2014;**63**:2016–25. <https://doi.org/10.1016/j.jacc.2014.02.581>
- Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004;**109**:2302–8. <https://doi.org/10.1161/01.CIR.0000126825.50903.18>
- Chin CWL, Shah ASV, McAllister DA, Joanna Cowell S, Alam S, Langrish JP, et al. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J* 2014;**35**:2312–21. <https://doi.org/10.1093/eurheartj/ehu189>
- Lindman BR, Breyley JG, Schilling JD, Vatterott AM, Zajarias A, Maniar HS, et al. Prognostic utility of novel biomarkers of cardiovascular stress in patients with aortic stenosis undergoing valve replacement. *Heart* 2015;**101**:1382–8. <https://doi.org/10.1136/heartjnl-2015-307742>
- Gardezi SK, Coffey S, Prendergast BD, Myerson SG. Serum biomarkers in valvular heart disease. *Heart* 2018;**104**:349–58. <https://doi.org/10.1136/heartjnl-2016-310482>
- Bach DS, Cimino N, Deeb GM. Unoperated patients with severe aortic stenosis. *J Am Coll Cardiol* 2007;**50**:2018–9. <https://doi.org/10.1016/j.jacc.2007.08.011>
- Eugène M, Duchnowski P, Prendergast B, Wendler O, Laroche C, Monin J-L, et al. Contemporary management of severe symptomatic aortic stenosis. *J Am Coll Cardiol* 2021;**78**:2131–43. <https://doi.org/10.1016/j.jacc.2021.09.864>
- Brennan JM, Lowenstern A, Sheridan P, Boero JJ, Hourani VH, Vemulapalli S, et al. Association between patient survival and clinician variability in treatment rates for aortic valve stenosis. *J Am Heart Assoc* 2021;**10**:e020490. <https://doi.org/10.1161/JAHA.120.020490>
- Flannery L, Etiwy M, Camacho A, Liu R, Patel N, Tavil-Shatelyan A, et al. Patient- and process-related contributors to the underuse of aortic valve replacement and subsequent mortality in ambulatory patients with severe aortic stenosis. *J Am Heart Assoc* 2022;**11**:e025065. <https://doi.org/10.1161/JAHA.121.025065>
- Li SX, Patel NK, Flannery LD, Selberg A, Kandanelly RR, Morrison FJ, et al. Trends in utilization of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol* 2022;**79**:864–77. <https://doi.org/10.1016/j.jacc.2021.11.060>
- Dzadzko V, Clavel MA, Dzadzko M, Medina-Inojosa JR, Michelena H, Maalouf J, et al. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet* 2018;**391**:960–9. [https://doi.org/10.1016/S0140-6736\(18\)30473-2](https://doi.org/10.1016/S0140-6736(18)30473-2)
- Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol* 2014;**63**:470–7. <https://doi.org/10.1016/j.jacc.2013.09.038>
- Mahabadi AA, Kahlert P, Kahlert HA, Dykun I, Balcer B, Forsting M, et al. Comparison of lipoprotein(a)-levels in patients  $\geq 70$  years of age with versus without aortic valve stenosis. *Am J Cardiol* 2018;**122**:645–9. <https://doi.org/10.1016/j.amjcard.2018.04.046>
- Girard A, Gaillard E, Puri R, Capoulade R, Chan KL, Paulin A, et al. Impact of C-reactive protein levels on lipoprotein(a)-associated aortic stenosis incidence and progression. *Eur Heart J Open* 2023;**3**:oead032. <https://doi.org/10.1093/ehjopen/oead032>
- Nazarzadeh M, Pinho-Gomes AC, Bidel Z, Dehghan A, Canoy D, Hassaine A, et al. Plasma lipids and risk of aortic valve stenosis: a Mendelian randomization study. *Eur Heart J* 2020;**41**:3913–20. <https://doi.org/10.1093/eurheartj/ehaa070>
- Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;**29**:630–4. [https://doi.org/10.1016/S0735-1097\(96\)00563-3](https://doi.org/10.1016/S0735-1097(96)00563-3)
- Chui MC, Newby DE, Panarelli M, Bloomfield P, Boon NA. Association between calcific aortic stenosis and hypercholesterolemia: is there a need for a randomized controlled trial of cholesterol-lowering therapy? *Clin Cardiol* 2001;**24**:52–5. <https://doi.org/10.1002/clc.4960240109>
- Poggio P, Songia P, Cavallotti L, Barbieri SS, Zanotti I, Arsenault BJ, et al. PCSK9 involvement in aortic valve calcification. *J Am Coll Cardiol* 2018;**72**:3225–7. <https://doi.org/10.1016/j.jacc.2018.09.063>
- Perrot N, Valerio V, Moschetta D, Boekholdt SM, Dina C, Chen HY, et al. Genetic and in vitro inhibition of PCSK9 and calcific aortic valve stenosis. *JACC Basic Transl Sci* 2020;**5**:649–61. <https://doi.org/10.1016/j.jacbt.2020.05.004>
- Bergmark BA, O'Donoghue ML, Murphy SA, Kuder JF, Ezhov MV, Ceška R, et al. An exploratory analysis of proprotein convertase subtilisin/kexin type 9 inhibition and aortic stenosis in the FOURIER trial. *JAMA Cardiol* 2020;**5**:709–13. <https://doi.org/10.1001/jamacardio.2020.0728>
- Iwahashi N, Nakatani S, Umemura S, Kimura K, Kitakaze M. Usefulness of plasma B-type natriuretic peptide in the assessment of disease severity and prediction of outcome after aortic valve replacement in patients with severe aortic stenosis. *J Am Soc Echocardiogr* 2011;**24**:984–91. <https://doi.org/10.1016/j.echo.2011.03.012>
- Gerber IL, Stewart RAH, Legget ME, West TM, French RL, Sutton TM, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. *Circulation* 2003;**107**:1884–90. <https://doi.org/10.1161/01.CIR.0000006053.79248.0C>
- Bergler-Klein J, Mundigler G, Pibarot P, Burwash IG, Dumesnil JG, Blais C, et al. B-type natriuretic peptide in low-flow, low-gradient aortic stenosis. *Circulation* 2007;**115**:2848–55. <https://doi.org/10.1161/CIRCULATIONAHA.106.654210>
- Lancellotti P, Magne J, Donal E, Davin L, O'Connor K, Rosca M, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol* 2012;**59**:235–43. <https://doi.org/10.1016/j.jacc.2011.08.072>
- Henri C, Dulgheru R, Magne J, Caballero L, Laarabi S, Davin L, et al. Impact of serial B-type natriuretic peptide changes for predicting outcome in asymptomatic patients with aortic stenosis. *Can J Cardiol* 2016;**32**:183–9. <https://doi.org/10.1016/j.cjca.2015.06.007>
- Gerber IL, Legget ME, West TM, Richards AM, Stewart RAH. Usefulness of serial measurement of N-terminal pro-brain natriuretic peptide plasma levels in asymptomatic patients with aortic stenosis to predict symptomatic deterioration. *Am J Cardiol* 2005;**95**:898–901. <https://doi.org/10.1016/j.amjcard.2004.11.053>
- Holmgren A, Ljungberg J, Hultdin J, Johansson B, Bergdahl IA, Näslund U, et al. Troponin T but not C reactive protein is associated with future surgery for aortic stenosis: a population-based nested case-referent study. *Open Heart* 2020;**7**:e001325. <https://doi.org/10.1136/openhrt-2020-001325>
- Røsjo H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes

- of cardiac function and anatomy. *Am J Cardiol* 2011;**108**:88–91. <https://doi.org/10.1016/j.amjcard.2011.02.346>
32. Lancellotti P, Dulgheru R, Magne J, Henri C, Servais L, Bouznad N, et al. Elevated plasma soluble ST2 is associated with heart failure symptoms and outcome in aortic stenosis. *PLoS One* 2015;**10**:e0138940. <https://doi.org/10.1371/journal.pone.0138940>
  33. van Driel BO, Schuldt M, Algül S, Levin E, Güclü A, Germans T, et al. Metabolomics in severe aortic stenosis reveals intermediates of nitric oxide synthesis as most distinctive markers. *Int J Mol Sci* 2021;**22**:3569. <https://doi.org/10.3390/ijms22073569>
  34. Bengel P, Elkenani M, Beuthner BE, Pietzner M, Mohamed BA, Pollok-Kopp B, et al. Metabolomic profiling in patients with different hemodynamic subtypes of severe aortic valve stenosis. *Biomolecules* 2023;**13**:95. <https://doi.org/10.3390/biom13010095>
  35. Surendran A, Edel A, Chandran M, Bogaert P, Hassan-Tash P, Kumar Asokan A, et al. Metabolomic signature of human aortic valve stenosis. *JACC Basic Transl Sci* 2020;**5**:1163–77. <https://doi.org/10.1016/j.jacbt.2020.10.001>
  36. Villar AV, García R, Merino D, Llano M, Cobo M, Montalvo C, et al. Myocardial and circulating levels of microRNA-21 reflect left ventricular fibrosis in aortic stenosis patients. *Int J Cardiol* 2013;**167**:2875–81. <https://doi.org/10.1016/j.ijcard.2012.07.021>
  37. Yang F, Liu S, Gu Y, Yan Y, Ding X, Zou L, et al. MicroRNA-22 promoted osteogenic differentiation of valvular interstitial cells by inhibiting CAB39 expression during aortic valve calcification. *Cell Mol Life Sci* 2022;**79**:146. <https://doi.org/10.1007/s00018-022-04177-6>
  38. Song R, Zhai Y, Ao L, Fullerton DA, Meng X. MicroRNA-204 deficiency in human aortic valves elevates valvular osteogenic activity. *Int J Mol Sci* 2019;**21**:76. <https://doi.org/10.3390/ijms21010076>
  39. Røsjø H, Dahl MB, Bye A, Andreassen J, Jørgensen M, Wisløff U, et al. Prognostic value of circulating microRNA-210 levels in patients with moderate to severe aortic stenosis. *PLoS One* 2014;**9**:e91812. <https://doi.org/10.1371/journal.pone.0091812>
  40. Chen Z, Li C, Xu Y, Li Y, Yang H, Rao L. Circulating level of miR-378 predicts left ventricular hypertrophy in patients with aortic stenosis. *PLoS One* 2014;**9**:e105702. <https://doi.org/10.1371/journal.pone.0105702>
  41. Imai K, Okura H, Kume T, Yamada R, Miyamoto Y, Kawamoto T, et al. C-reactive protein predicts severity, progression, and prognosis of asymptomatic aortic valve stenosis. *Am Heart J* 2008;**156**:713–8. <https://doi.org/10.1016/j.ahj.2008.04.011>
  42. Shelbya K, Arthur V, Yang Y, Dorbala P, Buckley L, Claggett B, et al. Large-scale proteomics identifies novel biomarkers and circulating risk factors for aortic stenosis. *J Am Coll Cardiol* 2024;**83**:577–91. <https://doi.org/10.1016/j.jacc.2023.11.021>
  43. Zheng KH, Tsimikas S, Pawade T, Kroon J, Jenkins WSA, Doris MK, et al. Lipoprotein(a) and oxidized phospholipids promote valve calcification in patients with aortic stenosis. *J Am Coll Cardiol* 2019;**73**:2150–62. <https://doi.org/10.1016/j.jacc.2019.01.070>
  44. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;**352**:2389–97. <https://doi.org/10.1056/NEJMoa043876>
  45. Capoulade R, Torzewski M, Mayr M, Chan KL, Mathieu P, Bossé Y, et al. ApoCIII-Lp(a) complexes in conjunction with Lp(a)-OxPL predict rapid progression of aortic stenosis. *Heart* 2020;**106**:738–45. <https://doi.org/10.1136/heartjnl-2019-315840>
  46. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J* 2022;**43**:3925–46. <https://doi.org/10.1093/eurheartj/ehac361>
  47. Sánchez PL, Santos JL, Kaski JC, Cruz I, Arribas A, Villacorta E, et al. Relation of circulating C-reactive protein to progression of aortic valve stenosis. *Am J Cardiol* 2006;**97**:90–3. <https://doi.org/10.1016/j.amjcard.2005.07.113>
  48. Capoulade R, Mahmut A, Tastet L, Arsenault M, Bédard É, Dumesnil JG, et al. Impact of plasma Lp-PLA2 activity on the progression of aortic stenosis: the PROGRESSA study. *JACC Cardiovasc Imaging* 2015;**8**:26–33. <https://doi.org/10.1016/j.jcmg.2014.09.016>
  49. Mohty D, Pibarot P, Després JP, Côté C, Arsenault B, Cartier A, et al. Association between plasma LDL particle size, valvular accumulation of oxidized LDL, and inflammation in patients with aortic stenosis. *Arterioscler Thromb Vasc Biol* 2008;**28**:187–93. <https://doi.org/10.1161/ATVBAHA.107.154989>
  50. Côté N, Couture C, Pibarot P, Després JP, Mathieu P. Angiotensin receptor blockers are associated with a lower remodelling score of stenotic aortic valves. *Eur J Clin Invest* 2011;**41**:1172–9. <https://doi.org/10.1111/j.1365-2362.2011.02522.x>
  51. Capoulade R, Clavel MA, Mathieu P, Côté N, Dumesnil JG, Arsenault M, et al. Impact of hypertension and renin-angiotensin system inhibitors in aortic stenosis. *Eur J Clin Invest* 2013;**43**:1262–72. <https://doi.org/10.1111/eci.12169>
  52. Lee S, Lee S-A, Choi B, Kim Y-J, Oh SJ, Choi H-M, et al. Dipeptidyl peptidase-4 inhibition to prevent progression of calcific aortic stenosis. *Heart* 2020;**106**:1824–31. <https://doi.org/10.1136/heartjnl-2020-317024>
  53. Mathieu P, Bouchareb R, Boulanger MC. Innate and adaptive immunity in calcific aortic valve disease. *J Immunol Res* 2015;**2015**:851945. <https://doi.org/10.1155/2015/851945>
  54. Liu S, Ngo DTM, Chong CR, Amarasekera AT, Procter NEK, Licari G, et al. Suppression of neutrophil superoxide generation by BNP is attenuated in acute heart failure: a case for “BNP resistance”. *Eur J Heart Fail* 2015;**17**:475–83. <https://doi.org/10.1002/ehf.242>
  55. Villacorta H, Maisel AS. Soluble ST2 testing: a promising biomarker in the management of heart failure. *Arq Bras Cardiol* 2016;**106**:145–52. <https://doi.org/10.5935/abc.20150151>
  56. Broch K, Ueland T, Nymo SH, Kjekshus J, Hulthe J, Muntendam P, et al. Soluble ST2 is associated with adverse outcome in patients with heart failure of ischaemic aetiology. *Eur J Heart Fail* 2012;**14**:268–77. <https://doi.org/10.1093/eurjhf/hfs006>
  57. Bayes-Genis A, de Antonio M, Vila J, Peñañiel J, Galán A, Barallat J, et al. Head-to-head comparison of 2 myocardial fibrosis biomarkers for long-term heart failure risk stratification: ST2 versus galectin-3. *J Am Coll Cardiol* 2014;**63**:158–66. <https://doi.org/10.1016/j.jacc.2013.07.087>
  58. Arrieta V, Jover E, Navarro A, Martín-Núñez E, Garaikoetxea M, Matilla L, et al. Soluble ST2 levels are related to replacement myocardial fibrosis in severe aortic stenosis. *Rev Española Cardiol (Engl Ed)* 2023;**76**:679–89. <https://doi.org/10.1016/j.rec.2022.12.007>
  59. Fabiani I, Conte L, Pugliese NR, Calogero E, Barletta V, Di Stefano R, et al. The integrated value of sST2 and global longitudinal strain in the early stratification of patients with severe aortic valve stenosis: a translational imaging approach. *Int J Cardiovasc Imaging* 2017;**33**:1915–20. <https://doi.org/10.1007/s10554-017-1203-2>
  60. Elmariah S, McCarthy C, Ibrahim N, Furman D, Mukai R, Magaret C, et al. Multiple biomarker panel to screen for severe aortic stenosis: results from the CASABLANCA study. *Open Heart* 2018;**5**:e000916. <https://doi.org/10.1136/openhrt-2018-000916>
  61. Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med* 2003;**349**:343–9. <https://doi.org/10.1056/NEJMoa022831>
  62. Van Belle E, Rauch A, Vincent F, Robin E, Kibler M, Labreuche J, et al. Von Willebrand factor multimers during transcatheter aortic-valve replacement. *N Engl J Med* 2016;**375**:335–44. <https://doi.org/10.1056/NEJMoa1505643>
  63. Van Belle E, Vincent F, Rauch A, Casari C, Jeanpierre E, Loobuyck V, et al. von Willebrand factor and management of heart valve disease: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:1078–88. <https://doi.org/10.1016/j.jacc.2018.12.045>
  64. Zeller J, Loeffel-Silver J, Khoshmanesh K, Baratchi S, Lai A, Nero TL, et al. Shear-sensing by C-reactive protein: linking aortic stenosis and inflammation. *Circ Res* 2024;**135**:1033–47. <https://doi.org/10.1161/CIRCRESAHA.124.324248>
  65. Arsenault BJ, Loganath K, Girard A, Botezatu S, Zheng KH, Tzolos E, et al. Lipoprotein(a) and calcific aortic valve stenosis progression: a systematic review and meta-analysis. *JAMA Cardiol* 2024;**9**:835–42. <https://doi.org/10.1001/jamacardio.2024.1882>
  66. Mahmut A, Boulanger MC, El Hussein D, Fournier D, Bouchareb R, Després JP, et al. Elevated expression of lipoprotein-associated phospholipase A2 in calcific aortic valve disease: implications for valve mineralization. *J Am Coll Cardiol* 2014;**63**:460–9. <https://doi.org/10.1016/j.jacc.2013.05.105>
  67. Côté N, Pibarot P, Pèpin A, Fournier D, Audet A, Arsenault B, et al. Oxidized low-density lipoprotein, angiotensin II and increased waist circumference are associated with valve inflammation in prehypertensive patients with aortic stenosis. *Int J Cardiol* 2010;**145**:444–9. <https://doi.org/10.1016/j.ijcard.2009.05.054>
  68. Carter-Storch R, Le Nezet E, Ali M, Powers A, Haujir A, Demers K, et al. Angiotensin II receptor blockers are associated with reduced valvular fibrosis in women with aortic stenosis. *Can J Cardiol* 2024;**40**:1690–9. <https://doi.org/10.1016/j.cjca.2024.03.009>
  69. Song J-K, Lee S, Kim Y-J, Kim H-K, Ha J-W, Choi E-Y, et al. Effect of evogliptin on the progression of aortic valvular calcification. *J Am Coll Cardiol* 2024;**84**:1064–75. <https://doi.org/10.1016/j.jacc.2024.06.037>
  70. Luo G, Ducey P, McKee MD, Pinero GJ, Loyer E, Behringer RR, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature* 1997;**386**:78–81. <https://doi.org/10.1038/386078a0>
  71. Gragnano F, Crisci M, Bigazzi MC, Bianchi R, Sperlongano S, Natale F, et al. Von Willebrand factor as a novel player in valvular heart disease: from bench to valve replacement. *Angiology* 2018;**69**:103–12. <https://doi.org/10.1177/0003319717708070>
  72. Jiang L, Wang J, Li R, Fang Z-M, Zhu X-H, Yi X, et al. Disturbed energy and amino acid metabolism with their diagnostic potential in mitral valve disease revealed by untargeted plasma metabolic profiling. *Metabolomics* 2019;**15**:57. <https://doi.org/10.1007/s11306-019-1518-1>
  73. Deroyer C, Magne J, Moonen M, Le Goff C, Dupont L, Hulin A, et al. New biomarkers for primary mitral regurgitation. *Clin Proteomics* 2015;**12**:25. <https://doi.org/10.1186/s12014-015-9097-2>
  74. Tan HT, Ling LH, Dolor-Torres MC, Yip JW-L, Richards AM, Chung MCM. Proteomics discovery of biomarkers for mitral regurgitation caused by mitral valve prolapse. *J Proteomics* 2013;**94**:337–45. <https://doi.org/10.1016/j.jpro.2013.10.009>
  75. Hojo Y, Kumakura H, Kanai H, Iwasaki T, Ichikawa S, Kurabayashi M. Lipoprotein(a) is a risk factor for aortic and mitral valvular stenosis in peripheral arterial disease. *Eur Heart J Cardiovasc Imaging* 2016;**17**:492–7. <https://doi.org/10.1093/ehjci/jev338>
  76. Kalfota M, Sigvardsen PE, Afzal S, Langsted A, Fuchs A, Kühl JT, et al. Elevated lipoprotein(a) in mitral and aortic valve calcification and disease: the Copenhagen General Population Study. *Atherosclerosis* 2022;**349**:166–74. <https://doi.org/10.1016/j.atherosclerosis.2021.11.029>
  77. Garg PK, Guan W, Karger AB, Steffen BT, Budoff M, Tsai MY. Lipoprotein (a) and risk for calcification of the coronary arteries, mitral valve, and thoracic aorta: the

- Multi-Ethnic Study of Atherosclerosis. *J Cardiovasc Comput Tomogr* 2021;**15**:154–60. <https://doi.org/10.1016/j.jcct.2020.06.002>
78. Detaint D, Messika-Zeitoun D, Avierinos JF, Scott C, Chen H, Burnett JC, et al. B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. *Circulation* 2005;**111**:2391–7. <https://doi.org/10.1161/01.CIR.0000164269.80908.9D>
  79. Magne J, Mahjoub H, Pierard LA, O'Connor K, Pirllet C, Pibarot P, et al. Prognostic importance of brain natriuretic peptide and left ventricular longitudinal function in asymptomatic degenerative mitral regurgitation. *Heart* 2012;**98**:584–91. <https://doi.org/10.1136/heartjnl-2011-301128>
  80. Magne J, Mahjoub H, Pibarot P, Pirllet C, Pierard LA, Lancellotti P. Prognostic importance of exercise brain natriuretic peptide in asymptomatic degenerative mitral regurgitation. *Eur J Heart Fail* 2012;**14**:1293–302. <https://doi.org/10.1093/eurjhf/hfs114>
  81. Clavel MA, Tribouilloy C, Vanoverschelde JL, Pizarro R, Suri RM, Szymanski C, et al. Association of B-type natriuretic peptide with survival in patients with degenerative mitral regurgitation. *J Am Coll Cardiol* 2016;**68**:1297–307. <https://doi.org/10.1016/j.jacc.2016.06.047>
  82. Pizarro R, Bazzino OO, Oberti PF, Falconi M, Achilli F, Arias A, et al. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. *J Am Coll Cardiol* 2009;**54**:1099–106. <https://doi.org/10.1016/j.jacc.2009.06.013>
  83. Klar U, Gabriel H, Bergler-Klein J, Pernicka E, Heger M, Mascherbauer J, et al. Prognostic value of serial B-type natriuretic peptide measurement in asymptomatic organic mitral regurgitation. *Eur J Heart Fail* 2011;**13**:163–9. <https://doi.org/10.1093/eurjhf/hfq189>
  84. Ogata F, Hanatani S, Nakashima N, Yamamoto M, Shirahama Y, Ishii M, et al. Human epididymis protein 4 is a useful predictor of post-operative prognosis in patients with severe aortic stenosis. *ESC Heart Fail* 2024;**11**:2924–32. <https://doi.org/10.1002/ehf2.14845>
  85. Chen M-C, Chang T-H, Chang J-P, Huang H-D, Ho W-C, Lin Y-S, et al. Circulating miR-148b-3p and miR-409-3p as biomarkers for heart failure in patients with mitral regurgitation. *Int J Cardiol* 2016;**222**:148–54. <https://doi.org/10.1016/j.ijcard.2016.07.179>
  86. Spinka G, Bartko PE, Pavo N, Freitag C, Zlabinger K, Prausmüller S, et al. Secondary mitral regurgitation-insights from microRNA assessment. *Eur J Clin Invest* 2021;**51**:e13381. <https://doi.org/10.1111/eci.13381>
  87. Duchnowski P, Hryniewiecki T, Kuśmierczyk M, Szymański P. The usefulness of selected biomarkers in aortic regurgitation. *Cardiol J* 2019;**26**:477–82. <https://doi.org/10.5603/CJ.a2018.0108>
  88. Pizarro R, Bazzino OO, Oberti PF, Falconi ML, Arias AM, Krauss JG, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. *J Am Coll Cardiol* 2011;**58**:1705–14. <https://doi.org/10.1016/j.jacc.2011.07.016>
  89. Chen S, Redfors B, O'Neill BP, Clavel MA, Pibarot P, Elmariah S, et al. Low and elevated B-type natriuretic peptide levels are associated with increased mortality in patients with preserved ejection fraction undergoing transcatheter aortic valve replacement: an analysis of the PARTNER II trial and registry. *Eur Heart J* 2020;**41**:958–69. <https://doi.org/10.1093/eurheartj/ehz892>
  90. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. *J Am Coll Cardiol* 2013;**62**:2329–38. <https://doi.org/10.1016/j.jacc.2013.08.1621>
  91. Zhang B, Xu H, Zhang H, Liu Q, Ye Y, Hao J, et al. Prognostic value of N-terminal pro-B-type natriuretic peptide in elderly patients with valvular heart disease. *J Am Coll Cardiol* 2020;**75**:1659–72. <https://doi.org/10.1016/j.jacc.2020.02.031>
  92. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;**40**:976–82. [https://doi.org/10.1016/S0735-1097\(02\)02059-4](https://doi.org/10.1016/S0735-1097(02)02059-4)
  93. Clerico A, Zaninotto M, Prontera C, Giovannini S, Ndreu R, Franzini M, et al. State of the art of BNP and NT-proBNP immunoassays: the CardioOrmoCheck study. *Clin Chim Acta* 2012;**414**:112–9. <https://doi.org/10.1016/j.cca.2012.07.017>
  94. Loganath K, Craig NJ, Everett RJ, Bing R, Tsampanian V, Molek P, et al. Early intervention in patients with asymptomatic severe aortic stenosis and myocardial fibrosis: the EVOLVED randomized clinical trial. *JAMA* 2025;**333**:213–21. <https://doi.org/10.1001/jama.2024.22730>
  95. Krau NC, Lünstedt NS, Freitag-Wolf S, Brehm D, Petzina R, Lutter G, et al. Elevated growth differentiation factor 15 levels predict outcome in patients undergoing transcatheter aortic valve implantation. *Eur J Heart Fail* 2015;**17**:945–55. <https://doi.org/10.1002/ehf2.318>
  96. Baldenhofer G, Zhang K, Spethmann S, Laule M, Eilers B, Leonhardt F, et al. Galectin-3 predicts short- and long-term outcome in patients undergoing transcatheter aortic valve implantation (TAVI). *Int J Cardiol* 2014;**177**:912–7. <https://doi.org/10.1016/j.ijcard.2014.10.010>
  97. Zhang H-L, Song G-Y, Zhao J, Wang Y-B, Wang M-Y, Xu Y-L, et al. Preprocedural circulating galectin-3 and the risk of mortality after transcatheter aortic valve replacement: a systematic review and meta-analysis. *Biosci Rep* 2020;**40**:BSR20202306. <https://doi.org/10.1042/BSR20202306>
  98. Cai A, Miyazawa A, Sunderland N, Piper SE, Gibbs TGJ, Wang D, et al. ST2 in patients with severe aortic stenosis and heart failure. *Cardiol J* 2021;**28**:129–35. <https://doi.org/10.5603/CJ.a2019.0052>
  99. Kirchhoff C, Habben I, Ivell R, Krull N. A major human epididymis-specific cDNA encodes a protein with sequence homology to extracellular proteinase inhibitors. *Biol Reprod* 1991;**45**:350–7. <https://doi.org/10.1095/biolreprod45.2.350>
  100. Hertlein L, Stieber P, Kirschenhofer A, Krockner K, Nagel D, Lenhard M, et al. Human epididymis protein 4 (HE4) in benign and malignant diseases. *Clin Chem Lab Med* 2012;**50**:2181–8. <https://doi.org/10.1515/clinm-2012-0097>
  101. Bingle CD, Vyakarnam A. Novel innate immune functions of the whey acidic protein family. *Trends Immunol* 2008;**29**:444–53. <https://doi.org/10.1016/j.it.2008.07.001>
  102. de Boer RA, Cao Q, Postmus D, Damman K, Voors AA, Jaarsma T, et al. The WAP four-disulfide core domain protein HE4: a novel biomarker for heart failure. *JACC Heart Fail* 2013;**1**:164–9. <https://doi.org/10.1016/j.jchf.2012.11.005>
  103. Piek A, Meijers WC, Schroten NF, Gansevoort RT, de Boer RA, Silljé HH. HE4 serum levels are associated with heart failure severity in patients with chronic heart failure. *J Card Fail* 2017;**23**:12–9. <https://doi.org/10.1016/j.cardfail.2016.05.002>
  104. Yamamoto M, Hanatani S, Araki S, Izumiya Y, Yamada T, Nakanishi N, et al. HE4 predicts progressive fibrosis and cardiovascular events in patients with dilated cardiomyopathy. *J Am Heart Assoc* 2021;**10**:e021069. <https://doi.org/10.1161/JAHA.120.021069>
  105. Hecht S, Giuliani C, Nuche J, Farjat Pasos JI, Bernard J, Tastet L, et al. Multimarker approach to improve risk stratification of patients undergoing transcatheter aortic valve implantation. *JACC Adv* 2024;**3**:100761. <https://doi.org/10.1016/j.jaccadv.2023.100761>
  106. García R, Villar AV, Cobo M, Llano M, Martín-Durán R, Hurlé MA, et al. Circulating levels of miR-133a predict the regression potential of left ventricular hypertrophy after valve replacement surgery in patients with aortic stenosis. *J Am Heart Assoc* 2013;**2**:e000211. <https://doi.org/10.1161/JAHA.113.000211>
  107. Dörr O, Walther C, Liebetrau C, Keller T, Sommer T, Boeder N, et al. Galectin-3 and ST2 as predictors of therapeutic success in high-risk patients undergoing percutaneous mitral valve repair (MitraClip). *Clin Cardiol* 2018;**41**:1164–9. <https://doi.org/10.1002/clc.22996>
  108. Galeone A, Lessana A, Mascolo E, Di Serio F, Marraudino N, Laborde F, et al. Interleukin-1 receptor-related protein ST2 and mitral valve repair outcome in patients with chronic degenerative mitral regurgitation. *Thorac Cardiovasc Surg* 2014;**62**:47–51. <https://doi.org/10.1055/s-0033-1356751>
  109. Clerico A, Carlo Zucchini G, Pilo A, Passino C, Emdin M. Clinical relevance of biological variation: the lesson of brain natriuretic peptide (BNP) and NT-proBNP assay. *Clin Chem Lab Med* 2006;**44**:366–78. <https://doi.org/10.1515/CCLM.2006.063>
  110. Gilard M, Eltchaninoff H, Lung B, Donzeau-Gouge P, Chevreuil K, Fajadet J, et al. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;**366**:1705–15. <https://doi.org/10.1056/NEJMoa1114705>
  111. Abdul-Jawad Altisent O, Puri R, Regueiro A, Chamandi C, Rodriguez-Gabella T, Del Trigo M, et al. Predictors and association with clinical outcomes of the changes in exercise capacity after transcatheter aortic valve replacement. *Circulation* 2017;**136**:632–43. <https://doi.org/10.1161/CIRCULATIONAHA.116.026349>
  112. Frank D, Stark S, Lutz M, Weissbrodt A, Freitag-Wolf S, Petzina R, et al. Preprocedural high-sensitive troponin predicts survival after transcatheter aortic valve implantation (TAVI). *Int J Cardiol* 2013;**169**:e38–9. <https://doi.org/10.1016/j.ijcard.2013.08.108>
  113. Chorianopoulos E, Krumdorf U, Geis N, Pleger ST, Giannitsis E, Katus HA, et al. Preserved prognostic value of preinterventional troponin T levels despite successful TAVI in patients with severe aortic stenosis. *Clin Res Cardiol* 2014;**103**:65–72. <https://doi.org/10.1007/s00392-013-0624-8>
  114. Köhler WM, Freitag-Wolf S, Lambers M, Lutz M, Niemann PM, Petzina R, et al. Preprocedural but not periprocedural high-sensitive troponin T levels predict outcome in patients undergoing transcatheter aortic valve implantation. *Cardiovasc Ther* 2016;**34**:385–96. <https://doi.org/10.1111/1755-5922.12208>
  115. Vidula MK, Orlenko A, Zhao L, Salvador L, Small AM, Horton E, et al. Plasma biomarkers associated with adverse outcomes in patients with calcific aortic stenosis. *Eur J Heart Fail* 2021;**23**:2021–32. <https://doi.org/10.1002/ehf.2361>
  116. Schmid J, Stojakovic T, Zweiker D, Scharnagl H, Maderthaler RD, Scherr D, et al. ST2 predicts survival in patients undergoing transcatheter aortic valve implantation. *Int J Cardiol* 2017;**244**:87–92. <https://doi.org/10.1016/j.ijcard.2017.06.066>
  117. Stundl A, Lünstedt NS, Courtz F, Freitag-Wolf S, Frey N, Holdenrieder S, et al. Soluble ST2 for risk stratification and the prediction of mortality in patients undergoing transcatheter aortic valve implantation. *Am J Cardiol* 2017;**120**:986–93. <https://doi.org/10.1016/j.amjcard.2017.06.033>
  118. Wernly B, Lichtenauer M, Jirak P, Eder S, Reiter C, Kammler J, et al. Soluble ST2 predicts 1-year outcome in patients undergoing transcatheter aortic valve implantation. *Eur J Clin Invest* 2017;**47**:149–57. <https://doi.org/10.1111/eci.12719>
  119. O'Leary JM, Clavel MA, Chen S, Goel K, O'Neill B, Elmariah S, et al. Association of natriuretic peptide levels after transcatheter aortic valve replacement with subsequent clinical outcomes. *JAMA Cardiol* 2020;**5**:1113–23. <https://doi.org/10.1001/jamacardio.2020.2614>

120. Husser O, Núñez J, Núñez E, Holzamer A, Camboni D, Luchner A, et al. Tumor marker carbohydrate antigen 125 predicts adverse outcome after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2013;**6**:487–96. <https://doi.org/10.1016/j.jcin.2013.02.006>
121. Schafer MJ, Atkinson EJ, Vanderboom PM, Kotajarvi B, White TA, Moore MM, et al. Quantification of GDF11 and myostatin in human aging and cardiovascular disease. *Cell Metab* 2016;**23**:1207–15. <https://doi.org/10.1016/j.cmet.2016.05.023>
122. Sinning JM, Wollert KC, Sedaghat A, Wiedera C, Radermacher MC, Descoups C, et al. Risk scores and biomarkers for the prediction of 1-year outcome after transcatheter aortic valve replacement. *Am Heart J* 2015;**170**:821–9. <https://doi.org/10.1016/j.ahj.2015.07.003>
123. Yamamoto M, Shimura T, Kano S, Kagase A, Kodama A, Sago M, et al. Prognostic value of hypoalbuminemia after transcatheter aortic valve implantation (from the Japanese Multicenter OCEAN-TAVI Registry). *Am J Cardiol* 2017;**119**:770–7. <https://doi.org/10.1016/j.amjcard.2016.11.019>
124. Spangenberg T, Budde U, Schewel D, Frerker C, Thielsen T, Kuck K-H, et al. Treatment of acquired von Willebrand syndrome in aortic stenosis with transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2015;**8**:692–700. <https://doi.org/10.1016/j.jcin.2015.02.008>
125. Natorska J, Bykowska K, Hlawaty M, Marek G, Sadowski J, Undas A. Increased thrombin generation and platelet activation are associated with deficiency in high molecular weight multimers of von Willebrand factor in patients with moderate-to-severe aortic stenosis. *Heart* 2011;**97**:2023–8. <https://doi.org/10.1136/hrt.2010.217273>
126. Aung N, Dworakowski R, Byrne J, Alcock E, Deshpande R, Rajagopal K, et al. Progressive rise in red cell distribution width is associated with poor outcome after transcatheter aortic valve implantation. *Heart* 2013;**99**:1261–6. <https://doi.org/10.1136/heartjnl-2013-303910>
127. Santos-Faria J, Gavina C, Rodrigues P, Coelho J, da Costa Martins P, Leite-Moreira A, et al. MicroRNAs and ventricular remodeling in aortic stenosis. *Rev Port Cardiol* 2020;**39**:377–87. <https://doi.org/10.1016/j.repc.2019.09.014>
128. Kofler M, Reinstadler SJ, Stastny L, Dumfarth J, Reindl M, Wachter K, et al. Prognostic implications of pre-procedural high-sensitivity cardiac troponin T in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2017;**10**:2345–6. <https://doi.org/10.1016/j.jcin.2017.09.020>
129. Fabiani I, Santoni T, Angelillis M, Petricciolo S, Colli A, Pellegrini G, et al. Growth differentiation factor 15 in severe aortic valve stenosis: relationship with left ventricular remodeling and frailty. *J Clin Med* 2020;**9**:2998. <https://doi.org/10.3390/jcm9092998>
130. Ternacle J, Hecht S, Eltchaninoff H, Salaun E, Clavel M-A, Côté N, et al. Durability of transcatheter aortic valve implantation. *EuroIntervention* 2024;**20**:e845–64. <https://doi.org/10.4244/EIJ-D-23-01050>
131. Rodriguez-Gabella T, Voisine P, Dagenais F, Mohammadi S, Perron J, Dumont E, et al. Long-term outcomes following surgical aortic bioprosthesis implantation. *J Am Coll Cardiol* 2018;**71**:1401–12. <https://doi.org/10.1016/j.jacc.2018.01.059>
132. Nollert G, Miksch J, Kreuzer E, Reichart B. Risk factors for atherosclerosis and the degeneration of pericardial valves after aortic valve replacement. *J Thorac Cardiovasc Surg* 2003;**126**:965–8. [https://doi.org/10.1016/S0022-5223\(02\)73619-2](https://doi.org/10.1016/S0022-5223(02)73619-2)
133. Ternacle J, Côté N, Krapf L, Nguyen A, Clavel M-A, Pibarot P. Chronic kidney disease and the pathophysiology of valvular heart disease. *Can J Cardiol* 2019;**35**:1195–207. <https://doi.org/10.1016/j.cjca.2019.05.028>
134. Tastet L, Pibarot P, Shen M, Clisson M, Côté N, Salaun E, et al. Oral anticoagulation therapy and progression of calcific aortic valve stenosis. *J Am Coll Cardiol* 2019;**73**:1869–71. <https://doi.org/10.1016/j.jacc.2019.01.043>
135. Salaun E, Mahjoub H, Girerd N, Dagenais F, Voisine P, Mohammadi S, et al. Rate, timing, correlates, and outcomes of hemodynamic valve deterioration after bioprosthetic surgical aortic valve replacement. *Circulation* 2018;**138**:971–85. <https://doi.org/10.1161/CIRCULATIONAHA.118.035150>
136. Lorusso R, Gelsomino S, Lucà F, De Cicco G, Billè G, Carella R, et al. Type 2 diabetes mellitus is associated with faster degeneration of bioprosthetic valve: results from a propensity score-matched Italian multicenter study. *Circulation* 2012;**125**:604–14. <https://doi.org/10.1161/CIRCULATIONAHA.111.025064>
137. Salaun E, Mahjoub H, Dahou A, Mathieu P, Larose É, Després J-P, et al. Hemodynamic deterioration of surgically implanted bioprosthetic aortic valves. *J Am Coll Cardiol* 2018;**72**:241–51. <https://doi.org/10.1016/j.jacc.2018.04.064>
138. Nsaibia MJ, Mahmut A, Mahjoub H, Dahou A, Bouchareb R, Boulanger M-C, et al. Association between plasma lipoprotein levels and bioprosthetic valve structural degeneration. *Heart* 2016;**102**:1915–21. <https://doi.org/10.1136/heartjnl-2016-309541>
139. Mahmut A, Mahjoub H, Boulanger M-C, Fournier D, Després J-P, Pibarot P, et al. Lp-PLA2 is associated with structural valve degeneration of bioprostheses. *Eur J Clin Invest* 2014;**44**:136–45. <https://doi.org/10.1111/eci.12199>
140. Lee S, Levy RJ, Christian AJ, Hazen SL, Frick NE, Lai EK, et al. Calcification and oxidative modifications are associated with progressive bioprosthetic heart valve dysfunction. *J Am Heart Assoc* 2017;**6**:e005648. <https://doi.org/10.1161/JAHA.117.005648>
141. Nsaibia MJ, Boulanger MC, Bouchareb R, Mkannez G, Dahou A, Salaun E, et al. Soluble CD14 is associated with the structural failure of bioprostheses. *Clin Chim Acta* 2018;**485**:173–7. <https://doi.org/10.1016/j.cca.2018.06.045>
142. Mahjoub H, Mathieu P, Larose E, Dahou A, Sénéchal M, Dumesnil J-G, et al. Determinants of aortic bioprosthetic valve calcification assessed by multidetector CT. *Heart* 2015;**101**:472–7. <https://doi.org/10.1136/heartjnl-2014-306445>
143. Aykan AÇ, Gökdeniz T, Kalçık M, Astarcıoğlu MA, Gündüz S, Karakoyun S, et al. Role of antidiolipin antibodies in the pathogenesis of prosthetic valve thrombosis: an observational study. *Herz* 2015;**40**:528–33. <https://doi.org/10.1007/s00059-013-4038-1>
144. Gürsoy OM, Karakoyun S, Kalçık M, Gökdeniz T, Yesin M, Gündüz S, et al. Usefulness of novel hematologic inflammatory parameters to predict prosthetic mitral valve thrombosis. *Am J Cardiol* 2014;**113**:860–4. <https://doi.org/10.1016/j.amjcard.2013.11.029>
145. Kibler M, Marchandot B, Messas N, Caspar T, Vincent F, Von Hunolstein JJ, et al. CT-ADP point-of-care assay predicts 30-day paravalvular aortic regurgitation and bleeding events following transcatheter aortic valve replacement. *Thromb Haemost* 2018;**118**:893–905. <https://doi.org/10.1055/s-0038-1639352>
146. Schewel E, Frerker C, Schewel J, Wohlmuth P, Meincke F, Thielsen T, et al. Clinical impact of paravalvular leaks on biomarkers and survival after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2015;**85**:502–14. <https://doi.org/10.1002/ccd.25295>
147. Ruiz CE, Hahn RT, Berrebi A, Borer JS, Cutlip DE, Fontana G, et al. Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis. *Eur Heart J* 2018;**39**:1224–45. <https://doi.org/10.1093/eurheartj/ehx211>
148. Dahou A, Clavel MA, Capoulade R, O'Connor K, Ribeiro HB, Côté N, et al. B-type natriuretic peptide and high-sensitivity cardiac troponin for risk stratification in low-flow, low-gradient aortic stenosis: a substudy of the TOPAS study. *JACC Cardiovasc Imaging* 2018;**11**:939–47. <https://doi.org/10.1016/j.jcmg.2017.06.018>
149. Lindman BR, Clavel MA, Abu-Alhayja'a R, Côté N, Dagenais F, Novak E, et al. Multimarker approach to identify patients with higher mortality and rehospitalization rate after surgical aortic valve replacement for aortic stenosis. *JACC Cardiovasc Interv* 2018;**11**:2172–81. <https://doi.org/10.1016/j.jcin.2018.07.039>