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Review

Unmet needs and knowledge gaps in aortic stenosis: A position paper from the Heart Valve Council of the French Society of Cardiology

Charles Fauvel[a], Augustin Coisne[b], Romain Capoulade[c], Corentin Bourg[d], Christelle Diakov[e], Sophie Ribeyrolles[e], Jérome Jouan[f], Thierry Folliguet[g], Marion Kibler[h], Julien Dreyfus[i], Julien Magne[j,n], Yohann Bohbot[k], Théo Pezel[l], Thomas Modine[m], Erwan Donal[d,*]

[a] *Cardiology Department, Rouen University Hospital, 76000 Rouen, France*
[b] *Institut Pasteur de Lille, CHU Lille, Lille University, INSERM, 59000 Lille, France*
[c] *L'Institut du Thorax, CHU Nantes, Nantes University, CNRS, INSERM, 44007 Nantes, France*
[d] *Department of Cardiology, CHU Rennes, University of Rennes, INSERM, LTSI - UMR 1099, 35000 Rennes, France*
[e] *Institut Mutualiste Montsouris, 75014 Paris, France*
[f] *Department of Cardiac and Thoracic Surgery, Limoges University Teaching Hospital, 87000 Limoges, France*
[g] *Department of Cardiac Surgery, Henri Mondor University Hospital, AP-HP, 94000 Créteil, France*
[h] *Department of Cardiovascular Surgery and Medicine, New Civil Hospital, CHU Strasbourg, Strasbourg University, 67000 Strasbourg, France*
[i] *Cardiology Department, Centre Cardiologique du Nord, 93200 Saint-Denis, France*
[j] *Department of Cardiology, Dupuytren Hospital, CHU Limoges, 87000 Limoges, France*
[k] *Department of Cardiology, Amiens University Hospital, 80054 Amiens, France*
[l] *Department of Radiology and Department of Cardiology, Lariboisière Hospital, AP–HP, Paris Cité University, 75010 Paris, France*
[m] *Department of Cardiology and Cardiovascular Surgery, Haut-Lévêque Cardiological Hospital, Bordeaux University Hospital, 33604 Pessac, France*
[n] *INSERM 1094, Limoges Faculty of Medicine, 87025 Limoges, France*

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ABSTRACT

Nowadays, valvular heart disease remains a significant challenge among cardiovascular diseases, affecting millions of people worldwide and exerting substantial pressure on healthcare systems. Within the spectrum of valvular heart disease, aortic stenosis is the most common valvular lesion in developed countries. Despite notable advances in understanding its pathophysiological processes, improved cardiovascular imaging techniques and expanding therapeutic options in recent years, there are still unmet needs and knowledge gaps regarding aortic stenosis pathophysiology, severity assessment, management and decision-making strategy. This review, prepared on behalf of the Heart Valve Council of the French Society of Cardiology, describes these gaps and future research perspectives to improve the outcome of patients with aortic stenosis.

1. Abbreviations

AS	aortic stenosis
AVA	aortic valve area
AVR	aortic valve replacement
CMR	cardiovascular magnetic resonance
LGE	late gadolinium enhancement
Lp(a)	lipoprotein(a)
LV	left ventricular
LVEF	left ventricular ejection fraction
PCSK9	proprotein convertase subtilisin/kexin type 9
RANKL	receptor activator of nuclear factor kB ligand
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement

2. Background

The field of heart valve diseases, especially the one focused on aortic stenosis (AS), has experienced incommensurable advances in recent years. Multiple innovative developments have emerged regarding decision-making processes and the diagnosis, management and treatment of patients with AS, coupled with a better

* Corresponding author. Cardiology Department, Rennes University Hospital, rue Henri Le Guillou, 35000 Rennes, France.
E-mail address: erwan.donal@chu-rennes.fr (E. Donal).

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understanding of the pathophysiology of this disease. However, there are still gaps in knowledge in the field. With this review, we aimed to highlight the main unmet needs regarding AS pathophysiology, severity assessment, timing for treatment referral and management strategy. We sought to consider the clinical needs, and to explore the pathophysiological targets that could impact how we might reconsider the management of patients with AS.

3. Epidemiology of AS

Although the prevalence of AS has been shown to increase with the aging of the population [1], its exact prevalence remains poorly defined. Marked geographical variations in AS prevalence have also been reported, probably influenced by genetics, lifestyle and environmental factors. The Framingham Heart Study estimated the prevalence of AS to be approximately 2% in individuals aged 60–69 years, and 4% among those aged 70–79 years. In a meta-analysis including subjects aged > 75 years, AS of any grade was estimated to affect 12.4% of the population [2]; of note, 3.4% of these subjects had severe AS, three quarters of whom were symptomatic. In the Valvular Heart Disease II survey, among the 5219 included patients with native severe valve disease, severe AS was present in 41.2% of cases, making it the most prevalent form of valvular heart disease [3].

As life expectancy continues to rise, the burden of AS is anticipated to increase exponentially. Additionally, the prevalence of AS may vary across different populations; some studies have suggested a higher prevalence in males compared with females [4]. Finally, the incidence of AS is also relatively understudied; the Tromsø Study reported an incidence rate of 4.9‰/year [5]. However, it is worth noting that the actual incidence and prevalence of AS are probably underestimated, and comprehensive population-based studies relying on echocardiography are scare, particularly in low- and middle-income countries. Benfari et al. recently showed that over 20 years, the incidence rate of AS remained stable (52.5 per 100,000 patient-years), but was associated with an absolute burden of incident cases as a result of population growth [4].

4. Pathophysiology of AS

AS is a progressive disorder, characterized by thickening and calcification of the aortic valve [3,6]. In recent decades, the pathophysiological mechanisms leading to fibrocalcification of the aortic valve leaflets have been studied extensively, highlighting potential therapeutic targets. However, to date, there are still gaps in knowledge that preclude the development of pharmacological therapy to stop (or at least slow down) the evolution of the pathology over time (Table 1).

Following the first exploration of AS genetics that established the familial aggregation of the disease in 2006 [7], several genetic studies have dissected the genetic architecture of the disease. These studies have provided compelling data supporting the involvement of genetic traits in the development of the disease, showing that AS is not a purely passive and degenerative disease, but rather the consequence of active mechanisms. The most recent and largest genome-wide association study, including 13,465 patients with AS and more than 640,000 controls, identified a total of 15 loci significantly and robustly associated with the disease; dyslipidaemia, inflammation, calcification and adiposity appeared to be the main contributors to fibrocalcification of the aortic valve [8]. These data corroborated the previously described pathways involved in AS [6], and emphasized their major roles in the development of AS, while offering the opportunity to identify therapeutic options for these patients.

The most promising therapeutic targets for AS are related to lipid metabolism, and especially to lipoprotein(a) (Lp(a)). Indeed, genetic and clinical studies have provided convincing evidence demonstrating a link between Lp(a) circulating concentration and AS development and progression [8–13]. Mechanistic studies have suggested that the detrimental effect of Lp(a) is mediated by its content in oxidized phospholipids [13–16]. These studies support the hypothesis that reducing circulating Lp(a) could be beneficial in modulating the progression of the disease.

In addition to Lp(a), recent evidence has reinforced the role of low-density lipoprotein cholesterol in the mineralization processes of the valve [8,17,18]. This hypothesis arose several years ago. AS was first described as an atherosclerotic-like disease, and lipid-lowering therapy based on statins appeared to be a promising therapeutic approach for these patients. However, randomized clinical trials testing the usefulness of statins in AS failed to demonstrate any effect on disease progression [19–22]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors appear to be the most promising option for patients with AS. PCSK9 acts as an endogenous inhibitor of the low-density lipoprotein receptor, via blockade of its recycling process at the membrane [23,24]. Recent evidence supports the potential benefit of PCSK9 inhibition in the context of AS [25–28], even if the precise mechanisms are still incompletely understood, and further mechanistic studies are needed to support the realization of randomized clinical trials focused on PCSK9 inhibitors in AS.

Several other pathways have been described in the processes leading to AS. The impact of immune cells and inflammation has been reported consistently [29]. Immune cells, particularly macrophages, are one of the most abundant cell types populating the valves, after valvular interstitial cells and valvular endothelial cells [29–31]. Exacerbated by endothelial dysfunction, immune cells invade the aortic valve tissue, and actively participate in fibrocalcification of the valve, via cytokine-mediated mechanisms and interactions with valvular interstitial cells/valvular endothelial cells [32–36], highlighting potential benefits for medications targeting inflammation and/or specific immune cells, as well as medications that restore or maintain endothelial function. Interestingly, clinical observations and association studies have pointed out that medications targeting the renin-angiotensin-aldosterone system could be beneficial in patients with AS, even if the precise underlying mechanisms of action of these drugs in the context of the valve remain elusive [37–43]. More recently, dipeptidyl peptidase-4 has been described as a mediator of valve calcification, and dipeptidyl peptidase-4 inhibition with gliptins should be evaluated [44,45]. Altogether, these data support a central role for interrelationships between valvular interstitial cells, valvular endothelial cells, immune cells and the proinflammatory microenvironment in the processes leading to aortic valve calcification.

Recent evidence highlights the accumulation of red blood cells into the diseased leaflets; these cells, particularly their iron content, promote valve calcification [46,47]. Interestingly, mechanistic studies focused on platelet-induced calcification have also recently outlined the previously reported clinical association between AS and platelet activation [48–52].

Finally, the mineralization of the valve is also conjointly mediated by phosphocalcic metabolism. Chronic kidney disease and osteoporosis–two clinical conditions associated with dysregulated phosphocalcic metabolism–have been associated with AS [53–55]. The receptor activator of nuclear factor kB (RANK)/RANK ligand (RANKL) axis, which regulates bone turnover, has been linked to calcification of the valve; RANKL is upregulated in AS and participates in the calcification processes via osteoblastic activation [56]. This concept of the “calcification paradox” was investigated in a recent randomized clinical trial looking at RANKL inhibitors (as well as bisphosphonates) to reduce the progression of AS [57]. The

Table 1
Pathophysiology of aortic stenosis: what we know and what we do not know.

What we know	What we don't know
AS is not only degenerative; genetic traits are involved	Primary hits that lead to the initiation of AS
Dyslipidaemia, inflammation, calcification and adiposity are the main pathways related to fibrocalcification of the valve	PCSK9 precise mechanisms in AS pathophysiology
Role of lipid metabolism – especially Lp(a) circulating concentration for AS development and progression	Benefit of lipid-lowering therapies focused on Lp(a) and/or PCSK9
	Effect of aggressive lifestyle modifications targeting visceral obesity and metabolic syndrome
Osteogenic differentiation of VICs	Role of renin-angiotensin-aldosterone system
Endothelial dysfunction (NO pathway) – inflammation and immune cell recruitment (especially macrophages), leading to a proinflammatory state	Crosstalk between valvular cells (i.e. VICs, VECs, immune cells, red blood cells) and associated mechanisms of aortic valve calcification
Role of red blood cells for VIC proliferation and calcification	Understanding of the calcification paradox leading to valve calcification
Upregulation of RANKL	Effect of DPP4 inhibitor
	Sex differences in AS pathophysiology

AS: aortic stenosis; DPP4: dipeptidyl peptidase-4; Lp(a): lipoprotein(a); NO: nitric oxide; PCSK9: proprotein convertase subtilisin/kexin type 9; RANKL: receptor activator of nuclear factor kB ligand; VEC: valvular endothelial cell; VIC: valvular interstitial cell.

study failed to demonstrate any significant effect of these pharmacological approaches in terms of reducing the progression of AS [57].

The significant advances in the understanding of the pathophysiological mechanisms leading to AS achieved in recent years identified AS as a multifaceted disease with complex and intricate pathophysiological mechanisms leading to valve calcification, with continuous feedback from each one to the others. These findings highlight the challenge we face in translating mechanistic data to the clinic and providing effective treatment for patients with AS. Research should be continued, to unravel all these mechanisms in depth, with the aim of determining the best approach to the pharmacological reduction of the progression of AS. Importantly, investigations looking at sex differences should be implemented systematically; data support differences in the mechanisms involved in the calcification of the valve between sexes, as well as medication efficacy, making this central to the development of AS treatment [35,58–60].

5. AS diagnosis

5.1. How to certify AS severity?

Echocardiography is, by definition, mandatory to ascertain AS severity, as it requires the combination of an aortic valve area (AVA) $\leq 1\,cm^2$ (or $\leq 0.6\,cm^2/m^2$), with a peak aortic jet velocity (V_{max}) ≥ 4 m/s and/or a mean pressure gradient ≥ 40 mmHg [61,62]. The inclusion of AVA in the definition is questionable, because in the presence of a high gradient without reversible high flow status, AS must be considered severe, even if the AVA is $> 1\,cm^2$ [62–64]. Nevertheless, this discrepancy is quite unusual (around 1% of cases [65]), whereas the association of an AVA $< 1\,cm^2$ with mean pressure gradient < 40 mmHg is much more frequent (3–30% according to various reports), and far more challenging [65–67]. When facing this situation, the first step is to rule out measurement errors, which are the main cause of inconsistent assessments [62,68]. The most common error relates to the assessment of the left ventricular (LV) outflow tract diameter, which can be difficult because of the presence of calcifications. In difficult cases, the formula of a size-adjusted LV outflow tract diameter reference value, proposed by Leye et al., can be used as a safeguard [69]. However, even when the two-dimensional echocardiographic measurement is accurate, it is still possible to obtain inconsistent results, because the LV outflow tract is rarely circular, but rather elliptical [70]. The second potential error is misplacement of the pulsed Doppler sample volume for LV outflow tract velocity time integral measurement, which must be placed 0.5–1 cm from the aortic valve [68]. Another classic pitfall is mean pressure gradient underestimation when a multiview approach (particularly the right parasternal view) is not performed, as a result of misalignment between the ultrasound beam and the aortic flow [68,71,72]. Finally, blood pressure should be measured during echocardiography to rule out a high blood pressure situation, and the recovery pressure phenomenon should be considered in the case of a small aorta [68,73–75].

After careful elimination of any measurement errors, if there is any persistent doubt about AS severity, other imaging techniques are required. In case of low flow, especially when related to LV dysfunction, dobutamine stress echocardiography can be performed to exclude pseudosevere AS and to look for contractile reserve, but its use requires expertise, and may be difficult, particularly in cases of atrial fibrillation [62,76]. The aortic valve calcium score, assessed by multislice computed tomography, is extremely useful, as severe AS is unlikely for a calcium score < 800 in women and < 1600 in men, but becomes likely above 1200 and 2000, and very likely when it exceeds 1600 and 3000, respectively [62,77]. Finally, in still inconclusive symptomatic cases with signs of severe AS, cardiac catheterization could be performed [62]. Fig. 1 depicts an algorithm for AS assessment.

5.2. How to improve AS risk stratification, and thus the timing of intervention?

It is now well accepted that AS treatment (either surgical [SAVR] or transcatheter [TAVR] aortic valve replacement) is recommended (Class I, level B) in symptomatic patients with high-gradient AS, regardless of LV ejection fraction (LVEF), or in symptomatic patients with severe low-flow (stroke volume index $\leq 35\,mL/m^2$) low-gradient (< 40 mmHg) AS with evidence of flow reserve on low-dose dobutamine echocardiography (Class I, level B). In patients with systolic dysfunction (LVEF < 50%) as a result of AS, even if asymptomatic, an intervention is recommended (Class I, level B), and should be considered without symptoms when LVEF is < 55% (Class IIa, level B; European guidelines) or < 60% (Class IIb, level B; American guidelines) [62,78,79].

As mortality increases with the severity of AS, it is also crucial to ask the question about early intervention in case of asymptomatic AS (Fig. 2). The current guidelines recommend considering earlier intervention in asymptomatic patients with very severe AS (mean gradient ≥ 60 mmHg or peak aortic jet velocity [V_{max}] > 5 m/s), in order to improve prognosis [62].

Exercise is good way to seek for symptoms and, consequently, an intervention is recommended if exercise testing demonstrates

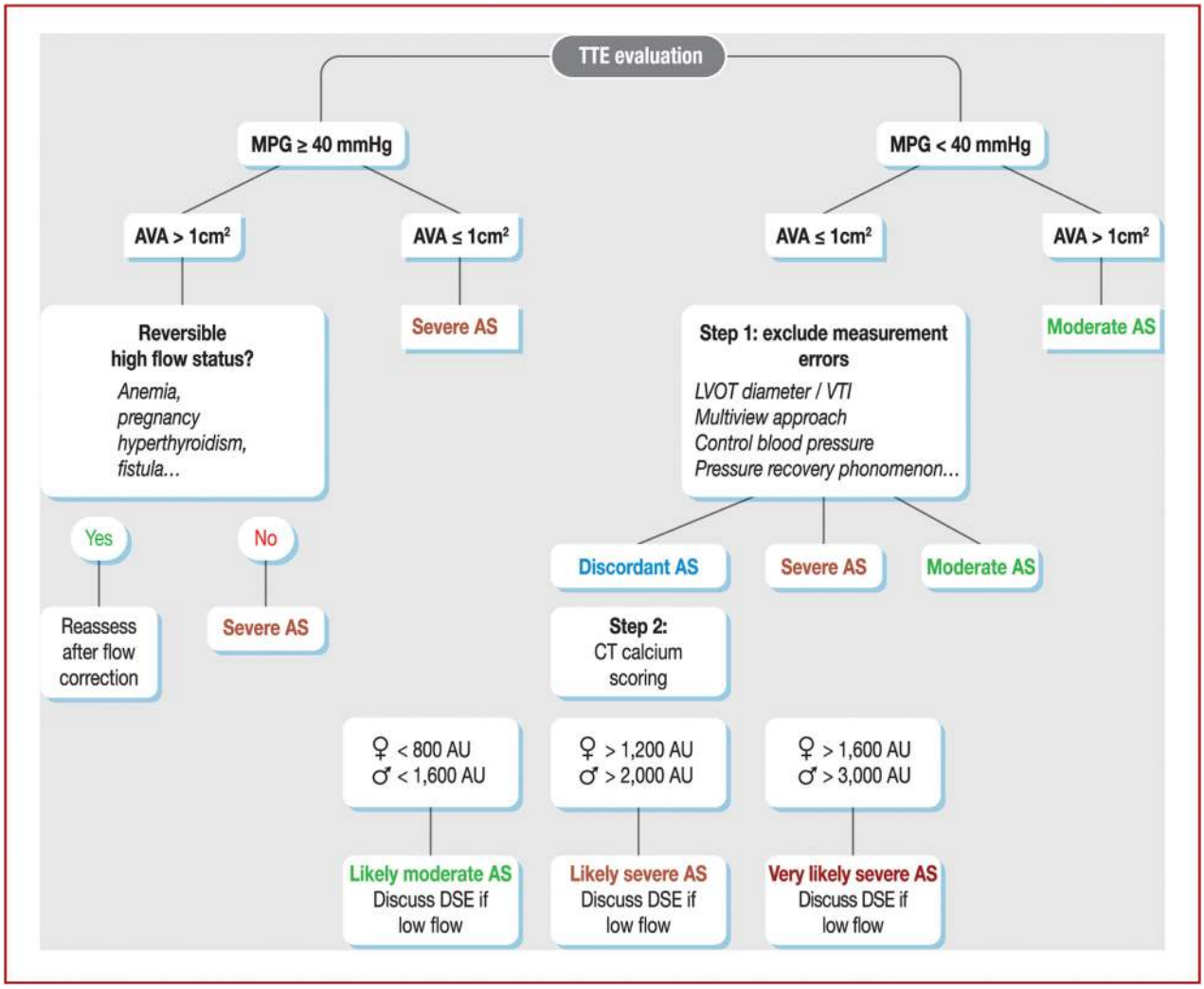


Fig. 1. Algorithm proposal for assessing aortic stenosis (AS) severity. AVA: aortic valve area; AU: Agatston unit; CT: computed tomography; DSE: dobutamine stress echocardiography; MPG: mean pressure gradient; LVOT: left ventricular outflow tract: TTE: transthoracic echocardiography; VTI: velocity time integral.

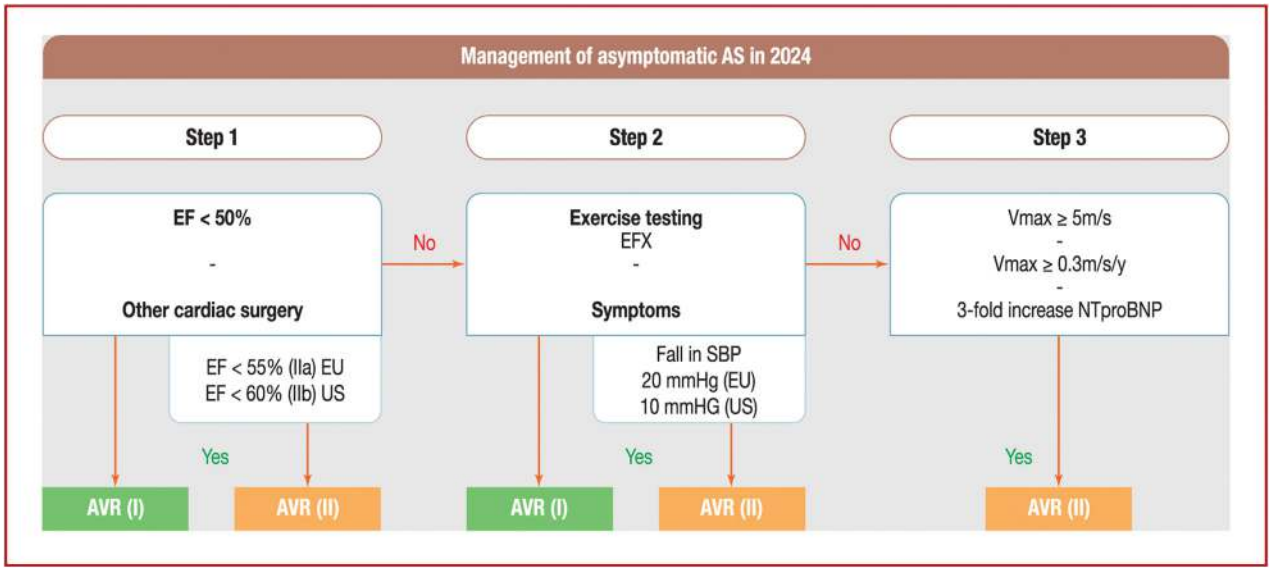


Fig. 2. Management of asymptomatic aortic stenosis (AS) in 2024 (adapted from Coisne et al. [78]). AVR: aortic valve replacement; EF: ejection fraction; EFX: functional exercise test; EU: European guidelines; NTproBNP: N-terminal prohormone of brain natriuretic peptide; SBP: systolic blood pressure; US: American guidelines; V_{max}: peak aortic jet velocity.

symptoms (Class I, level B) or if there is a sustained fall in systolic blood pressure during exercise testing (> 20 mmHg in the European guidelines, but > 10 mmHg in the American guidelines; Class IIa, level C). Beyond exercise stress echocardiography, cardiopulmonary exercise testing may be useful to detect patients with false asymptomatic AS, but also for prognosis assessment [80]. Additionally, patients with asymptomatic AS with low surgical risk and disease progression (i.e. peak velocity progression ≥ 0.3 m/s/year) and the presence of extensive calcifications on cardiac chest tomography [81–83] or in case of elevated natriuretic peptide concentration (> 3× age- and sex-corrected normal range) confirmed by repeated measurements, and no other explanation, should be referred for aortic valve replacement (AVR) (Class IIa, level B) [84,85]. Of note, in patients with moderate AS undergoing other cardiac surgery, AVR is indicated (Class IIa, level C for European guidelines; Class IIb, level C for American guidelines).

Several studies have drawn attention to other variables that could improve AS risk stratification (Table 2). For instance, a LV global longitudinal strain of < 15% is associated with reduced survival in asymptomatic patients with normal LVEF and severe AS [86]. Additionally, left atrial dilatation (> 50 mL/m^2) [87], stroke volume index < 30 mL/m^2 [88], LV hypertrophy [89] and right ventricular dysfunction (tricuspid annular plane systolic excursion [TAPSE] < 17 mm) [90] have been reported to worsen prognosis.

Similarly, the presence of fibrosis on cardiac magnetic resonance (CMR) (late gadolinium enhancement [LGE]) is associated with poorer long-term outcome [91]. Everett et al. showed that midwall LGE accumulates rapidly and is irreversible after AVR, suggesting prompt AVR in these patients [91]. CMR not only provides data for quantification of AVA (using phase-contrast assessment of the flow), but also gives information regarding the effects of AS on the left ventricle that are of prognostic significance: characterization of LV remodelling (before and after AVR); and quantification of LV fibrosis using LGE and myocardial T1 mapping [92]. Beyond "standard" valvular and myocardial assessment, four-dimensional flow CMR provides advanced flow quantification, allowing visualization and quantification of aortic flow pattern, flow displacement, wall shear stress and turbulent energy kinetics that are associated with aortic wall remodelling and aortopathy development [93]. This modality could be helpful in the future in case of discrepancies with echocardiography variables [94]. Although CMR will not replace transthoracic echocardiography, it appears to be efficient in stratifying patients according to their myocardial fibrosis pattern and evolution after AVR.

All of these data strongly reinforce that physicians should not only "look at the valve", but also "look at the myocardium" [95,96]. Accordingly, Généreux et al. proposed a staging classification that looks at the effects of AS on the left ventricle (stage 1), on the mitral valve or the left atrium (stage 2), on the presence of pulmonary hypertension or moderate-to-severe tricuspid regurgitation (stage 3) and, finally, on right ventricular dysfunction (stage 4) [97]. The higher the stage, the higher the 1-year mortality, suggesting that attention should be paid not only to the aortic valve, but also to "cardiac damage" for the timing of intervention. Indeed, even if these variables are not part of the guidelines, they should make us consider a closer follow-up (every 3 to 6 months) of these patients. Of note, specific attention to the co-diagnosis of cardiac amyloidosis is of crucial importance in terms of prognosis [98,99]. This classification has been validated in patients with symptomatic severe AS [100] and in those with severe AS undergoing TAVR [101], but also in patients with asymptomatic moderate-to-severe AS [102]. More recently, the incremental prognostic value of LV global longitudinal strain, mitral regurgitation and right ventricle to pulmonary artery coupling above the aforementioned staging classification showed interesting results [103,104]. Sex difference is another unmet and important issue, as recent data showed undertreatment resulting in excessive mortality in women with AS [105].

Finally, and knowing that patients with moderate AS (1 < AVA ≤ 1.5 cm^2) have poorer survival outcomes compared with the general population and patients with mild AS [106–110], it seems legitimate to challenge the current definition of AS severity, and future research should focus on this issue.

6. Is there still room for non-interventional management?

Left untreated, symptomatic and severe AS bears a disastrous prognosis [111]. Although AVR is the standard of care for patients with symptomatic severe AS, it is sometimes not feasible, and the question of medical management must be addressed, embodied by the hopes of treatments targeting the pathophysiology of AS [98,112,113]. This issue must be raised for patients ineligible (temporary or indefinitely) for AVR (either TAVR or SAVR) because they are considered high risk (through scores or anatomical criteria), patients who have refused AVR (raising the importance of appropriate medical information), those awaiting AVR and pregnant women. More importantly, the early stage of AS is a potential target, to reduce the progression of valve obstruction and delay or obviate the need for AVR.

As already mentioned above (Pathophysiology of AS), some medical treatments must be highlighted, as they could have relevance for AVR-ineligible patients, but also at early stage of the disease. To date, none has proven its efficiency or is recommended by any guidelines. Several treatments have been considered to be potentially able to reduce AS progression and/or its effects on myocardial performance, and some are being tested in ongoing randomized clinical trials.

Stressing similarities between the atherosclerosis process and the progression of AS, experimental and retrospective clinical studies have shown that lipid-lowering therapies could be effective in slowing AS progression. However randomized clinical trials focused on statin therapy have failed to prove effectiveness in reducing haemodynamic progression and aortic valve calcification or improving clinical outcomes [19,22,114]. Reduction of apolipoprotein B-containing lipoprotein particles – such as Lp(a) – could be beneficial through inhibition of leaflet calcification, thickening or cholesterol accumulation, as well as lowering macrophage infiltration. A randomized clinical trial (ClinicalTrials.gov identifier: NCT05646381) has been launched in patients with AS to confirm the clinical benefit of Lp(a) inhibition in the reduction of AS progression.

Metabolic syndrome and the dysmetabolism associated with visceral obesity have also been identified as potential contributors to the progression of AS [115–117]. However, neither aggressive treatment of metabolic syndrome nor lifestyle modifications has been assessed in prospective studies and, therefore, should be addressed in the future.

Renin-angiotensin-aldosterone system inhibitors have pleiotropic effects on the myocardium, going beyond afterload reduction, and might reduce the profibrotic process [113]. Randomized clinical trials are ongoing (ARBAS; ClinicalTrials.gov identifier: NCT04913870).

Targeting glucose-insulin homeostasis with dipeptidyl peptidase-4 inhibitors could slow endothelial dysfunction, leading to osteogenic mechanisms, and thiazolidinediones could reduce advanced glycation end products, exerting anti-inflammatory effects [44].

Inhibition of phosphodiesterase-5 could prevent and reverse cardiac remodelling by biventricular unloading in patients with AS [118,119]. One clinical study with sildenafil, a nitric oxide-independent soluble guanylate cyclase activator, showed reduction

Table 2
"Classical" and "new" aortic stenosis prognostic markers.

Variables	Source	*n*	Mortality impact
"Classical" AS markers			
LVEF	Bohbot et al. (2019) JACC CVI	1678	LVEF < 55% with no or minimal symptoms associated with poor outcome
	Capoulade et al. (2016) Heart	1065	LVEF independently associated with mortality
	Lancellotti et al. (2018) JAMA Cardiol	1375	LVEF < 60% in severe AS independently associated with all-cause and cardiovascular mortality
PAV > 5.5 m/s	Lancellotti et al. (2018) JAMA Cardiol	1375	HR 2.05, 95% CI 1.01–4.16; *P* = 0.046
Peak velocity progression ≥ 0.3 m/s/year	Rosenhek et al. (2000) NEJM	126	79% rate of surgery because of new symptoms or death within 2 years
Extensive calcifications on CCT	Pawade et al. (2018) Circ CVI	210	HR 3.90, 95% CI 2.19–6.78; *P* < 0.001
Elevated BNP > 3 N (age and sex-matched)	Clavel et al. (2014) J Am Coll Cardiol	1953	Overall: HR 2.43, 95% CI 1.94–3.05; *P* = 0.0001; asymptomatic: HR 3.93, 95% CI 2.40–6.43; *P* = 0.0001
AV calcification degree ≥ 1200 AU in women/ ≥ 2000 AU in men	Pawade et al. (2018) Circ CVI	918	AUC = 0.92 in women/0.89 in men
"New" AS markers			
Mean TVAG > 60 mmHg or PAV > 5 m/s	Bohbot et al. (2017) J Am Heart Assoc	1143	HR 1.71, 95% CI 1.33–2.20; *P* < 0.001
	Lancellotti et al. (2018) JAMA Card	1375	HR 2.05, 95% CI 1.01–4.16; *P* = 0.046
LV GLS < –14.7%	Magne et al. (2019) JACC CVI	1067	HR 2.62, 95% CI 1.66–4.13; *P* < 0.0001
Left ventricular hypertrophy	Cioffi et al. (2011) Heart	209	HR 3.08, 95% CI 1.65–5.73; *P* < 0.001
LA dilatation > 50 mL/m^2	Rusinaru et al. (2017) JAHA	1351	HR 1.42, 95% CI 1.08–1.91; *P* = 0.035
SVi < 30 mL/m^2	Rusinaru et al. (2018) Eur Heart J	1450	HR 1.60, 95% CI 1.17–2.18; *P* < 0.01
CMR fibrosis–LGE	Musa et al. (2018) Circulation	674	HR 2.39, 95% CI 1.40–4.05; *P* = 0.001
RV dysfunction (TAPSE < 17 mm)	Bohbot et al. (2020) Circ CVI	2181	Adjusted HR 1.55, 95% CI 1.21–1.97; *P* < 0.001
Sex category: women	Tribouilloy et al. (2021) J Am Heart Assoc	2429 (49.5% women)	5-year survival compared with expected survival: 62 ± 2% vs 71% for women (and 69 ± 1% vs 71% for men)

AS: aortic stenosis; AU: Agatston unit; AV: aortic valve; BNP: brain natriuretic peptide; CCT: cardiac chest tomography; CI: confidence interval; CMR: cardiovascular magnetic resonance; GLS: global longitudinal strain; HR: hazard ratio; LA: left atrium; LGE: late gadolinium enhancement; LV: left ventricle; LVEF: left ventricular ejection fraction; N: normal; PAV: peak aortic velocity; RV: right ventricle; SVi: stroke volume index; TAPSE: tricuspid annular plane systolic excursion; TVAG: transvalvular aortic gradient.

of aortic calcifications in a preclinical study [120], and an early stage clinical study is ongoing with ataciguat (ClinicalTrials.gov identifier: NCT02481258).

Targeting haemodynamics, with reduction of blood pressure and heart rate, might be associated with slowing down disease progression. Antihypertensive therapy is the only pharmacotherapy recommended in patients with AS by current American and European guidelines [62,121], both emphasizing careful titration and monitoring. Small prospective clinical studies have suggested that nitrates can be used to lower blood pressure in patients with AS, without excessive risk [37,122]. In acutely decompensated AS with heart failure, it is reasonable to use carefully titrated vasodilator therapy.

Genetic drivers are also a potential target. Cadherin 11 is overexpressed in mice with AS, driven by suppression of the NOTCH1 pathway [123]. Further testing of new strategies for targeting this pathway is therefore a strong lead to explore.

Molecular phenotyping also seems promising for identifying novel therapeutic targets. Follow-up and query of large databases with serial quantitative echocardiographic data could provide hypotheses for new targets to be tested in prospective randomized clinical trials [112].

Non-invasive ultrasound therapy is a new disruptive technology that involves the delivery of precise and focused ultrasound pulses to exert a reparative effect on the leaflets of the aortic valve. The objective of the ultrasound system developed is to act on embedded calcifications, and produces tissue softening through dense energetic cavitary bubble clouds generated by short ultrasound pulses of very high pressure. By softening the calcified valve tissues, non-invasive ultrasound therapy helps to restore leaflet mobility, and might improve the overall clinical status of patients with calcified AS. Recently, a single arm series of 40 patients was reported, and gives us hope in a new area of AS management. Confirmation studies are needed, but the outcome is perhaps not a fatality for someone who has AS [124].

7. Surgical and interventional treatment

7.1. Where have we come from and where are we now?

Over the past two decades, there has been a clear shift regarding the mode of intervention for AS. Indeed, based on the successive results of the PARTNER 1, 2 and 3 trials, showing the non-inferiority of TAVR compared with SAVR, there has been a progressive reduction in the age at which TAVR can be considered compared with SAVR [125–127]. Consequently, the number of TAVRs has increased linearly, even surpassing the number of SAVRs, which is now decreasing [128].

According to the European guidelines, TAVR is now recommended in older patients (≥ 75 years), and in those who are at high risk (Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM]/EuroSCORE II > 8%) or are otherwise unsuitable for surgery (Class I, level A) and SAVR [62]. Controversially, in the American Heart Association/American College of Cardiology guidelines, this

threshold has been lowered to the age of 65 years (Class I, level A) [79].

In any case, these two guidelines reinforce the value of "Heart Valve Centres", with local expertise and a structured collaborative "Heart Team" approach, including interventional imaging cardiologists and cardiac surgeons, as the central place for a shared-decision process with the patient (i.e. "patient-centred approach") [129].

7.2. Where are we going to?

SAVR is a Class I indication for patients with symptomatic severe AS. However, the AVATAR trial (Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis) showed a significant reduction in all-cause death, acute myocardial infarction, stroke or unplanned hospitalization for heart failure compared with conservative treatment in patients with severe asymptomatic AS, supporting early AVR in these patients, regardless of symptoms [130]. The same issue will be addressed by the ongoing EARLY TAVR trial, but using TAVR versus conservative management [131].

As SAVR and TAVR are indicated in a large spectrum of patients (from young to elderly), long-term lifetime management of patients with severe AS has become one of the most important topics to be discussed at Heart Team meetings. As neatly summarized by De Backer and Sondergaard, in the PARTNER 2B trial, the majority of patients were still alive > 10 years after SAVR, and at that time, surgical valve type and size for hypothetic future valve-in-valve TAVR were not at the centre of the discussion [132]. Yet, patient prosthesis mismatch is associated with poorer long-term outcome [133]. This issue reinforces the value of the "Valvular Heart Team", including not only cardiologists and surgeons, but also expertise in cardiac computed tomography.

The "natural" evolution of the European and American guidelines raises the question of "TAVR for all". Yet, the central issue that arises after lowering the age for TAVR indication is transcatheter bioprosthesis durability compared with SAVR [134]. Several mid-term studies did not show warning signs in terms of structural valve deterioration rate, but had discrepancies regarding the definition of durability before the implementation of the Valve Academic Research Consortium 3 (VARC-3) criteria [135–137]. Interestingly, long-term registries (i.e. > 5 years of follow-up) also showed a low severe structural valve deterioration rate [134] among patients who underwent TAVR and, more recently, the 8-year analysis of the NOTION trial (low-risk patients treated by either TAVR or SAVR) even showed a lower structural valve deterioration rate in TAVR compared with SAVR [138]. Consequently, the number of patients with late structural valve deterioration will probably increase in the future, and redo TAVR appears an acceptable option [139]. In parallel to TAVR extension, other issues have to be overcome, such as guaranteed permanent access to the coronary artery, management of paravalvular leak and conduction disorders [140].

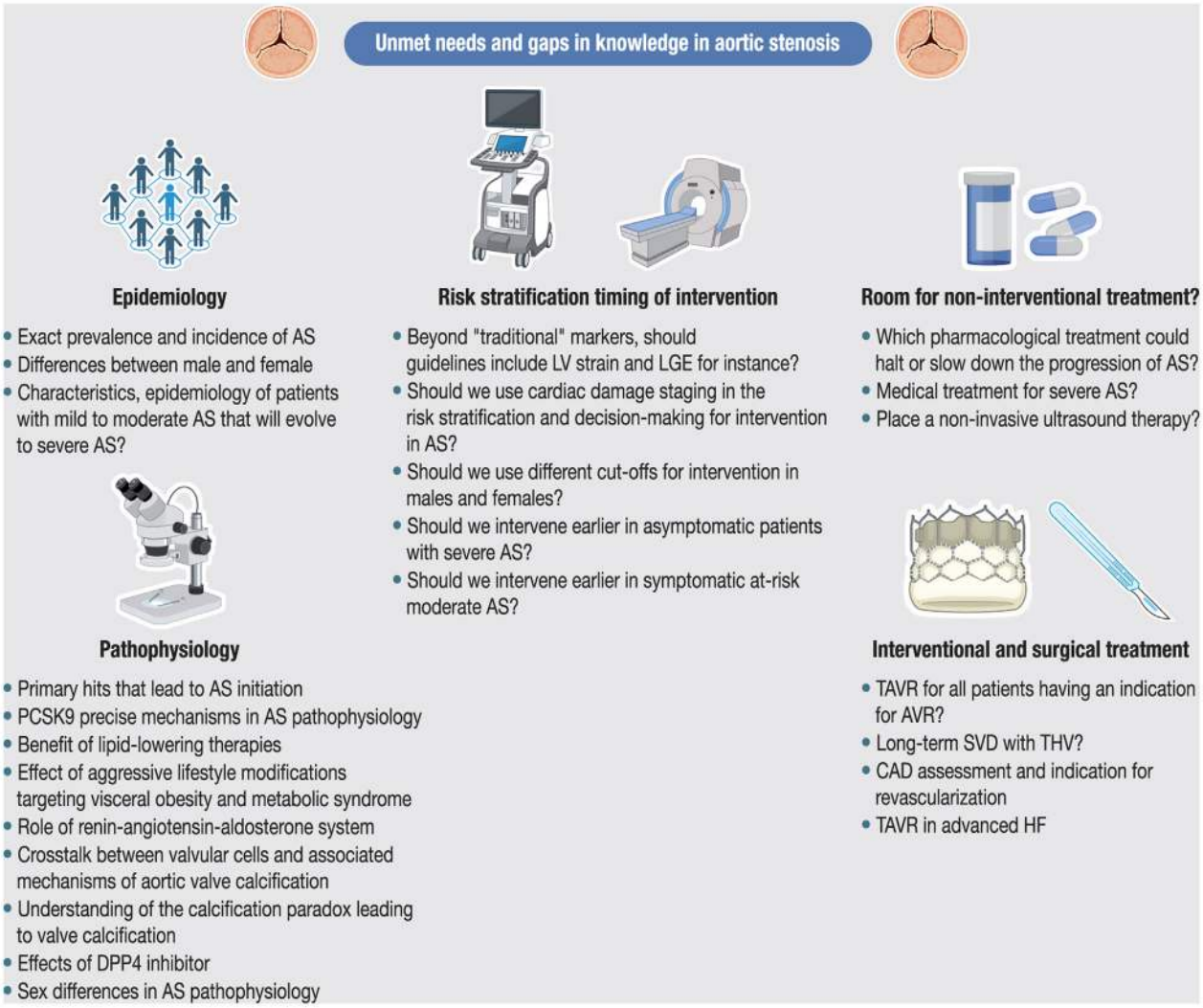
Another important condition to be considered is the presence of coronary artery disease in patients undergoing TAVR (ranging from 20% to 80%), as its assessment and indication for invasive treatment remain a matter of debate [141]. Importantly, transcatheter heart valve selection may also have an impact on future coronary access, and perprocedural commissural alignment is an important part of the procedure.

The Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure (TAVR UNLOAD) study (ClinicalTrials.gov identifier: NCT02661451) will address the value of TAVR in patients with advanced heart failure.

The Prospective Randomized Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement (PROGRESS) (ClinicalTrials.gov identifier: NCT04889872) and the EXPAND TAVR II trial (ClinicalTrials.gov identifier: NCT05149755) will investigate whether TAVR can improve outcomes in patients with moderate AS.

8. Perspectives and conclusions

With the ongoing aging of the population, the burden of AS is likely to increase, and the need for prevention, before intervention becomes the only option, must be addressed. With the help of medical societies and in collaboration with patient organizations, early detection and improvements in screening are mandatory, and will be achieved by raising awareness among physicians and the public about the burden and consequences of AS. Tools validated to detect AS at an earlier stage must emerge, and research to clarify the pathophysiology of AS will identify promising targets, leading to the testing of potential treatments. Randomized clinical trials must be designed to move the frontier from hopeful targets to efficient medical therapies. Beyond education of physicians and patients, the improvement in timely intervention should be endorsed by dedicated valvular heart disease clinics and valvular heart disease centres of excellence in the future, where patients' features (i.e. cardiovascular co-morbidities, medical history), AS severity and also cardiac damage must be at the heart of the discussion, in order to propose precise and personalized medicine (Central illustration).



Central illustration. Unmet need and knowledge gaps in aortic stenosis (AS). CAD: coronary artery disease; DPP4: dipeptidyl peptidase-4; HF: heart failure; LGE: late gadolinium enhancement; LV: left ventricle; PCSK9: proprotein convertase subtilisin/kexin type 9; SVD: structural valve deterioration; TAVR: transcatheter aortic valve replacement; THV: transcatheter heart valve.

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The authors declare that they have no competing interest.

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