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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AS = aortic stenosis
AF = atrial fibrillation
AR = aortic regurgitation
AV = aortic valve
AVA = aortic valve area
AVAi = aortic valve area index
AVC = aortic valve calcium
AVR = aortic valve replacement
BMI = body mass index
BNP = brain natriuretic peptide
BSA = body surface area
CA = cardiac amyloidosis
CAD = coronary artery disease
CO = cardiac output
CSA = cross sectional area
CT = computed tomography
CW = continuous wave
DLG-SAS = discordant low gradient severe aortic stenosis
ECM = extracellular matrix
ECV = extracellular volume
EOA = effective orifice area
FR = flow rate
GFR = glomerular filtration rate
GLS = global longitudinal strain
GOA = geometric orifice area
HFpEF = heart failure with preserved function
HG-SAS = high-gradient severe aortic stenosis
HU = Hounsfield unit
IPW = inverse probability weighting
IQR = interquartile range
LDL-c = low density lipoprotein cholesterol
LV = left ventricular
LVEDD = left ventricle end-diastolic diameter
LVEF = left ventricular ejection fraction
LVESD = left ventricle end-systolic diameter
LVOT = left ventricular outflow track
MAS = moderate aortic stenosis
MG = mean gradient
MMP = matrix metalloproteinase
MR = mitral regurgitation
MS = mitral stenosis
NYHA = New York Heart Association
PET = positron emission tomography
PG = pic gradient
PPM = patient-prothesis mismatch
PV = pic velocity
RCT = randomized controlled trial
RMST = restricted mean survival time
SAS = severe aortic stenosis
SAVR = surgical aortic valve replacement
SET = systolic ejection time
SPAP = systolic pulmonary arterial pressure
SR = sinus rhythm
SV = stroke volume
SVi = stroke volume index
TAVI = transcatheter aortic valve implantation
TEE = transesophageal echocardiography
TR = tricuspid regurgitation
TTE = transthoracic echocardiography
VEC = valvular endothelial cell
VHD = valvular heart disease
VIC = valvular interstitial cell
VIV = Valve-in-valve
VOI = volume of interest
VTI = velocity time integral

Part 1. AORTIC STENOSIS: GENERAL INTRODUCTION

Aortic stenosis (AS) is defined as the progressive narrowing of the aortic valve, leading to obstruction of the left ventricular outflow and reduced cardiac output. It is a major public health problem with high prevalence and is responsible for significant morbidity and mortality [(1)].

Its main cause is degenerative, characterized by the progressive thickening and calcification of the aortic valve leaflets [(2)]. To date, there is still no pharmacological treatment that prevents or halts the progression of the disease, with surgical or percutaneous aortic valve replacement (AVR) representing the only therapy that improves patient prognosis. Since this intervention is not without risks, it is important to select those patients who will benefit most from it. This is especially important given that once AS becomes severe and symptomatic, rate of survival drops dramatically [(3)]. Patients must therefore be carefully monitored over time to detect its progression and propose appropriate treatment in a timely manner. Accurate assessment of AS severity is therefore of paramount importance in the decision-making process. However, the severity of aortic stenosis is determined by the evaluation of several echocardiographic parameters.

Severe aortic stenosis (SAS) in its typical form, is characterized by an aortic valve area (AVA) <1.0 cm^2 or an indexed AVA (AVAi) <0.6 cm^2/m^2 and a mean gradient (MG) >40 mmHg [(4,5)]. However, clinicians frequently observe lower-than-expected peak transvalvular velocities and mean pressure gradients (MG ≤40 mmHg) despite the presence of SAS defined by AVA (<1.0 m^2). Since transvalvular pressure gradients are flow-dependent, it has long been recognized that patients with left ventricular (LV) dysfunction and low cardiac output may present low MG despite SAS [(6)]. Several recent studies have also indicated that these discrepancies can be observed in the absence of left ventricular dysfunction, and a "low flow" state is observed in only half of these patients [(7)]. The clinical significance of these particular entities (discordant aortic stenosis: surface area <1cm^2 and mean gradient <40 mmHg) is widely debated.

Once the severity of the disease has been diagnosed, the clinical and cardiac repercussions need to be investigated in order to propose an intervention. However, numerous studies have established that symptoms or deterioration in cardiac systolic function secondary to AS have a major impact on prognosis, even after AVR [8,9]. Since these different markers of severity appear late in the disease's progression, the debate and resultant discourse has now turned to the ideal timing for intervention. The challenge stems from the fact that AVR does not fully resolve the patient's condition—it mitigates a life-threatening disease in the short term but introduces a less severe, yet persistent, issue in the medium term. Prosthesis durability and operative risks therefore play a crucial role in assessing potential benefits and risks when surgery is proposed, especially in an asymptomatic patient with normal heart function. This is even more important when close follow-up could be a safe alternative [10]. Additionally, other prognostic factors are emerging in AS, particularly when evaluating the myocardial impacts of SAS. Indicators such as left atrial dilation or new-onset atrial fibrillation are proving to be valuable in guiding clinicians toward earlier intervention [11,12].

Clinicians require new markers to provide the best possible care for their patients. As such, the use of metabolic imaging with positron emission tomography (PET) is currently being explored due to the potential it offers concerning the identification of inflammatory and calcific activity within the valve. Moreover, the intensity of these pathophysiological processes is directly correlated with the risk of disease progression and cardiovascular events [13]. Cardiac CT scan, on the other hand, provides valuable insights into the severity of AS and its prognosis [14]. However, it only detects already-formed macrocalcifications, offering no information about the current activity of the disease [15].

Given the ongoing controversy surrounding the prognosis of AS, particularly in its discordant forms, we aimed to deepen our understanding of AS prognosis. Additionally, we sought to explore the potential role of advanced functional PET-CT imaging in evaluating disease progression. My work will

take you into the fascinating world of AS, shedding light on its prognosis, underlying pathophysiological features (e.g microcalcification process), and how these insights could be harnessed in future clinical practice.

Part 2. AORTIC STENOSIS: THEORETICAL BACKGROUND

2.1. Normal aortic valve

This section provides a concise overview of the anatomy and physiology of a normal aortic valve.

2.1.1. Anatomy and function

The human heart contains four valves that ensure unidirectional blood flow from one cardiac chamber to another. The aortic valve is located between the left ventricular outflow tract and the ascending aorta (**Figure 1**). Its primary function is to open during systole, thereby permitting oxygenated blood to circulate to the organs, and to close during diastole to prevent retrograde flow. The aortic valve opens and closes passively, responding to changes in pressure gradients within the left ventricle.

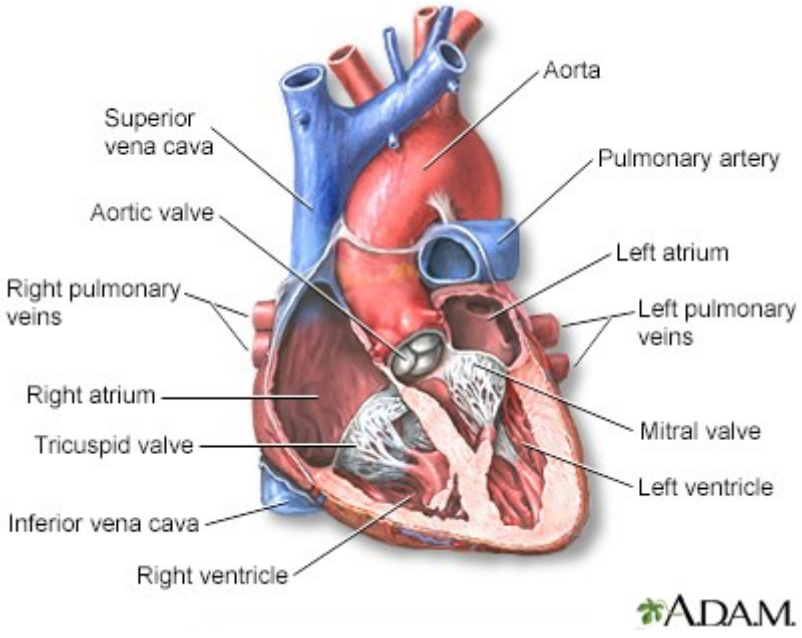


Figure 1: Location of the aortic valve in the heart. From A.D.A.M [(16)].

The aortic valve is structurally composed of semilunar cusps or leaflets, an annulus, and commissures. Usually it has three leaflets (tricuspid valve), named according to the presence of coronary ostia: the left coronary cusp, the non-coronary cusp, and the right coronary cusp. The annulus serves as the basal insertion point for the leaflets and is primarily composed of collagen; however, the term "annulus" is most often used to refer to the virtual ring passing through the nadirs of the different cusps. The commissures function as the upper attachment points of the cusps to the ascending aorta (**Figure 2**) with the sophisticated structure and tricuspid design of the aortic valve ensuring the optimal distribution of hemodynamic stress throughout the cardiac cycle. Consequently, any alteration in its geometry often leads to impaired function. The normal opening area of the valve in adults is approximately 3–4 cm^2 [(17)].

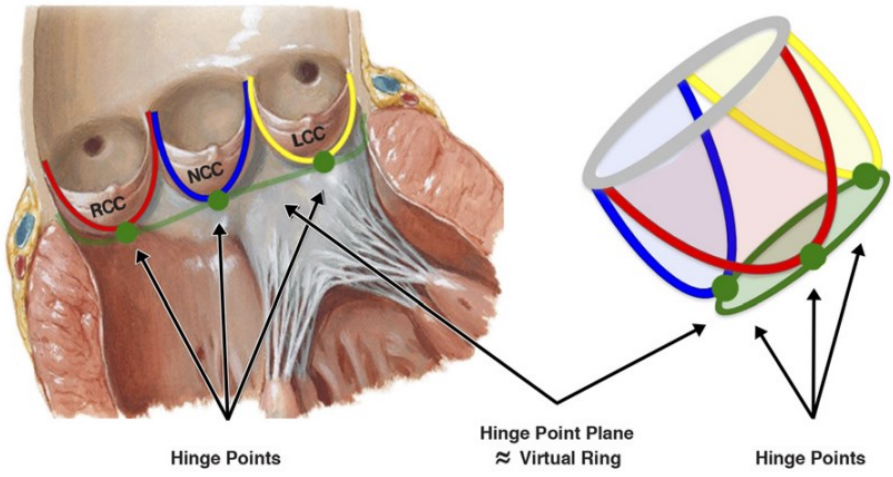


Figure 2: Anatomy of a normal aortic valve. LCC: left coronary cusp, NCC: non-coronary cusp, RCC: right coronary cusp. The green line represents the virtual ring or annulus, while the green points represent the three anatomical anchor points at the base of the attachments of the three cusps. Adapted from Kasel et al. JACC Cardiovasc Imaging 2013;6:249-62 [(18)].

2.1.2. Physiology and histology

Normal valve leaflets are avascular and thin, measuring less than one millimeter in thickness. They consist of an endothelium on both sides and an interstitium comprising three distinct, interactive layers: the lamina fibrosa, the spongiosa, and the ventricularis (**Figure 3**).

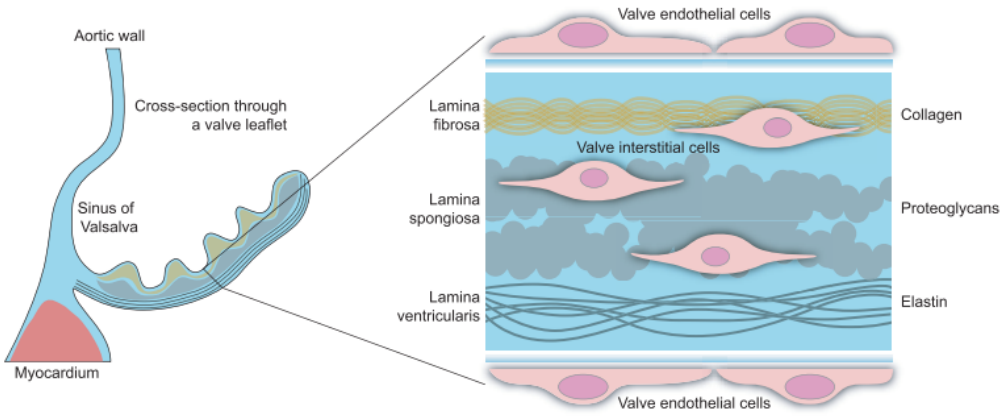


Figure 3: Simplified structure of the aortic valve leaflets. The cross section through the valve shows the trilayered organization of the extracellular matrix and the localization of the aortic valve endothelial cells (VECs) and interstitial cells (VICs). Adapted from Rutkovski et al. J Am Heart Assoc. 2017;6:e006339 [(19)].

The endothelium, located on both the aortic and ventricular sides, serves as an interface between the aortic valve (AV) and circulating blood. It plays a critical role in maintaining valve homeostasis by regulating permeability, modulating the adhesion of inflammatory cells, and mediating paracrine signaling. This regulation limits the infiltration of inflammatory cells and lipid accumulation in the valve structure [(20)].

The internal layers of the interstitium are densely populated with valvular interstitial cells (VIC) and an abundant extracellular matrix (ECM), providing

the leaflets with structural strength and elasticity [19,21]. For optimal function, the ECM must exhibit precise structural properties.

The lamina fibrosa, the thickest layer, is located on the aortic side of the valve and contains a high density of type I and III collagen fibers. This layer is crucial for providing essential load-bearing support to the valve [19,21].

The lamina ventricularis, situated on the ventricular side, contains type I collagen and elastin fibers oriented radially. These elastin fibers reduce radial strain and facilitate rapid compression during valve opening, thereby promoting efficient leaflet movement [19,21].

Positioned between the fibrosa and ventricularis, the lamina spongiosa is predominantly composed of glycosaminoglycans (GAGs) and proteoglycans. This layer functions as a foam-like buffer, absorbing mechanical energy and lubricating adjacent layers [19,21].

Valve interstitial cells (VICs) are distributed throughout the aortic valve's three layers. These cells are tightly integrated, producing the extracellular matrix and facilitating its ongoing remodeling and repair. This is primarily achieved by expressing matrix-degrading enzymes, such as matrix metalloproteinases (MMPs), along with their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs) [22]. In healthy valves, most VICs are quiescent and fibroblast-like, while a small portion (less than 5%) consists of myofibroblasts and smooth muscle cells [23,24]. However, VICs have been demonstrated to respond dynamically to alterations in their surrounding matrix and hemodynamic environment through a variety of specific signaling molecules [25]. Notably, VICs exhibit high phenotypic plasticity, enabling them to transition between different states during processes such as valve remodeling, injury, or disease [24,25].

2.2. Aortic stenosis

In this section, we will provide a brief overview of AS, covering its definition, etiology, epidemiology, pathophysiology, as well as diagnosis and treatment.

2.2.1. Definition

Aortic valve stenosis is characterized by a pathological and progressive decrease in the valve's opening capacity due to leaflet restriction, which creates a chronic obstruction of the left ventricular outflow tract (**Figure 4**). This obstruction leads to a sustained increase in LV afterload, resulting in inadequate cardiac output, decreased exercise capacity, and, if left untreated, ultimately heart failure and death.

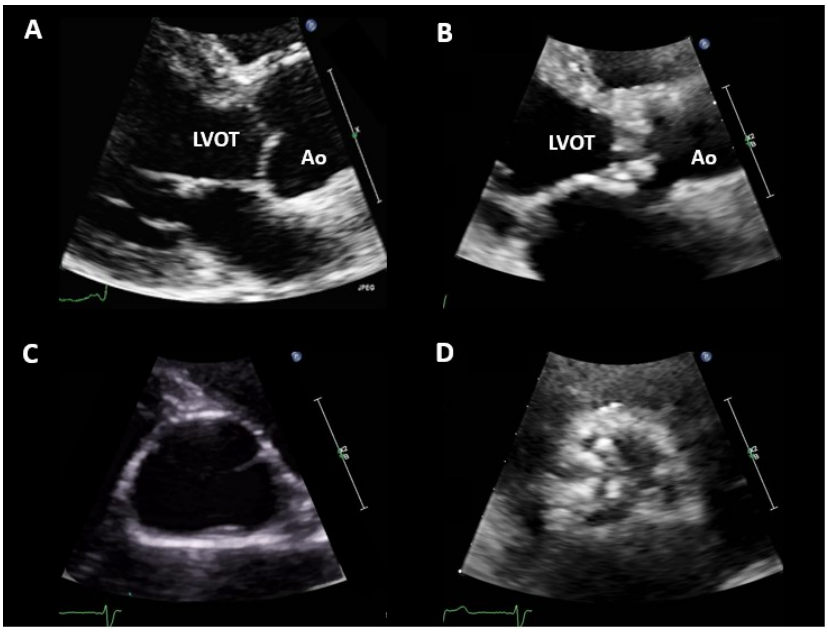


Figure 4: Echocardiographic images depicting 2D long-axis views (upper panels) and short-axis views (lower panels) of the aortic valve: normal anatomy is shown in the left panels, while severe calcification is illustrated in the right panels. Ao = ascending aorta; LVOT = left ventricle outflow track.

2.2.2. Etiology and risk factors

The causes of aortic stenosis can be divided into two categories: acquired and congenital (**Figure 5)**.

Acquired forms principally include degenerative and rheumatic causes.

Degenerative or calcified AS is by far the most common form observed in western countries. This condition is characterized by the accumulation of calcium deposits primarily located at the basal and central portions of the leaflets, resulting in a star-shaped narrowing of the valve opening. Its pathophysiology will be discussed in greater detail in Part 2.2.4.

Rheumatic AS is a narrowing of the aortic valve caused by rheumatic heart disease, which typically occurs following an untreated or poorly managed streptococcal infection. Rheumatic fever can elicit a cross-reactive autoimmune response targeting various organs, including valvular tissue (most often the aortic and/or mitral valves). This condition is characterized by commissural fusion, resulting in a triangular valve opening and thickening at the free edges of the cusps. While rheumatic AS is less common in western countries due to the widespread use of antibiotics, it remains a significant health concern in areas where rheumatic fever is more prevalent.

Other less common causes include radiation-induced AS resulting from high-dose chest radiation therapy, inflammatory diseases (such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis), metabolic disorders like Paget's disease, and infective endocarditis.

Congenital forms of AS include unicuspid, bicuspid, or quadricuspid valves, which most often manifest clinically in the early stages of life.

The Bicuspid aortic valve is an anatomical variation with a prevalence of approximately 0.5% to 2% [(26)]. The fusion of the right and left coronary cusps is the most commonly observed presentation, occuring in about 80% of

cases [27]. Patients with this condition tend to develop severe valvular stenosis at a younger age (<65 years) due to an altered distribution of mechanical stress on the valve. This prevalence of early-onset stenosis accounts for the fact that 50-75% of affected individuals will eventually require valve replacement [28]. This condition is more prevalent in males, with a male-to-female ratio of 3:1 [26].

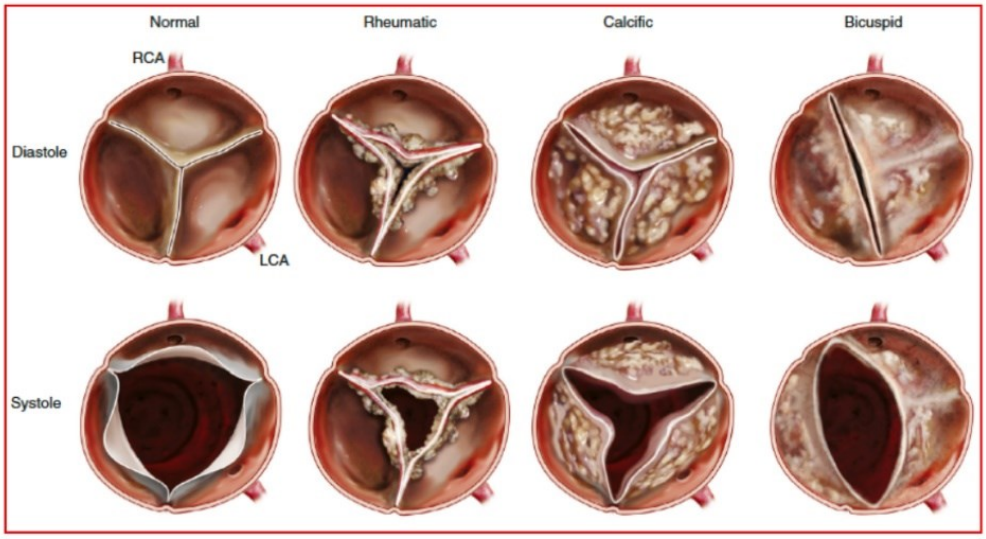


Figure 5: Etiology of Aortic Stenosis: morphology of calcified aortic stenosis, bicuspid valve, and rheumatic origin. Adapted from Baumgartner et al., J Am Soc Echocardiogr 22(1): 1-23;101-102 [17].

Numerous risk factors are associated with the development and progression of non-rheumatic calcified aortic stenosis, whether acquired or arising in the presence of a bicuspid valve. The main factors include age and sex, as well as those commonly found in vascular atherosclerosis [29], such as hypertension, smoking, obesity, diabetes, dyslipidemia, chronic kidney disease, pro-inflammatory states and imbalances in calcium-phosphate metabolism. More recently, lipoprotein(a) has been recognized as an important contributing factor due to its pro-inflammatory and pro-calcifying effects [30,31].

2.2.3. Epidemiology

Calcified aortic stenosis is the most common valvular heart disease in the Western world. Its prevalence is approximately 0.2% among adults aged 50 to 59; however, it significantly increases to 9.8% in individuals in their eighties, with an overall prevalence of 2.8% among adults over the age of 75 [32]. Valvular sclerosis, which is characterized by leaflet thickening and calcium deposits without hemodynamic obstruction, is even more prevalent, affecting up to 20-30% of individuals over 65 years of age and around 50% of those over 85 [33].

The VHD II survey conducted by the European Society of Cardiology's EURObservational Research Programme evaluated the management of valvular heart disease (VHD) across 28 ESC countries, involving 7247 patients with a mean age of 71 years (IQR 62-80) across 222 centers [34]. Of the 5219 patients with native VHD, 72.4% had single left-sided lesions, with AS being the most prevalent (41.2%), followed by mitral regurgitation (MR, 21.3%), aortic regurgitation (AR, 5.3%), and mitral stenosis (MS, 4.5%). Multiple left-sided VHD was observed in 24.9% of cases, while isolated right-sided VHD was present in 2.7%. **Figure 6** summarizes the causes of left-sided native VHD, with degenerative pathogenesis accounting for 67.8% of cases, followed by rheumatic heart disease at 11.8%.

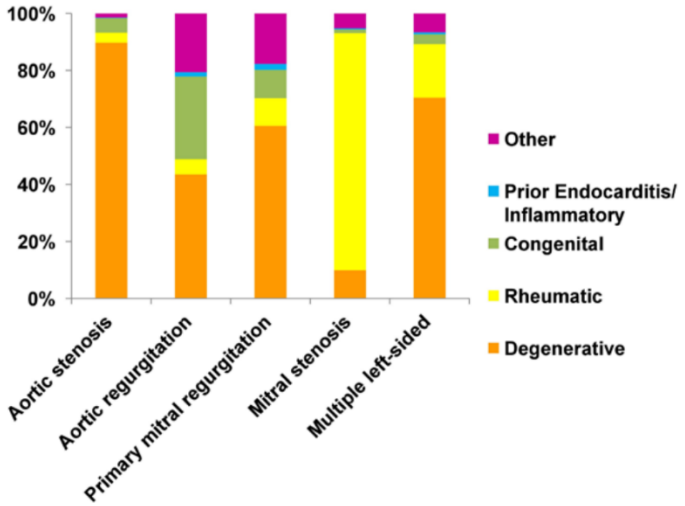


Figure 6: Types of left-sided native VHD. Adapted from Lung et Al. Circulation2000; 101: 1940 - 1946 [34]

Due to its high prevalence, AS is a major public health problem, significantly contributing to morbidity and mortality worldwide. Vaduganathan et al. assessed the global burden of cardiovascular diseases and demonstrated in a worldwide analysis across 204 countries that non-rheumatic calcified aortic valve stenosis ranks as the 11th leading cause of cardiovascular death [35].

2.2.4. Pathogenesis: the cellular perspective

For decades, aortic stenosis was thought to result merely from the passive wear and tear of the valve over time. Currently, it is well-established that aortic stenosis results from various (dys-)coordinated cellular and molecular processes (**Figure 7**).

Although the full range of mechanisms involved has not yet been completely understood, many of the key processes have been identified. The most widely accepted model explaining the pathophysiology of calcific aortic valve disease includes two distinct phases [36]:

- An **initial phase**, similar to vascular atherosclerosis, involving endothelial dysfunction, lipid deposition, and infiltration by inflammatory cells [36-39]. This phase mainly involves inflammatory processes and the activation of the VICs.

- A **propagation phase**, mediated by those VICs that develop an osteoblast-like phenotype, similar to skeletal bone and also promote progressive fibrosis of the extracellular matrix [19,36,38,39].

During the **initial phase**: early lesions are characterized by endothelial dysfunction, chronic lipid, and inflammatory infiltrates, as well as microcalcifications and fibrosis.

Endothelial damage and dysfunction is believed to result from hemodynamic forces that exert mechanical stress on the valvular microenvironment. This stress is more pronounced on the aortic side of the valve and at various basal flexion points of the cusps, explaining why these areas are typically the first to develop calcifications. Cardiovascular risk factors or structural modifications of the valve, such as a bicuspid aortic valve, exacerbate these mechanical stresses and promote endothelial damage. Endothelial dysfunction triggers a range of metabolic changes, including reduced synthesis of intercellular tight junctions that weaken the endothelial barrier, thereby increasing permeability and allowing for lipoprotein passage and inflammatory cell infiltration [(40)]. Additionally, decreased expression of endothelial nitric oxide synthase (eNOS) further diminishes a regulatory mechanism that normally inhibits the osteoblastic differentiation of interstitial cells and the calcification of the extracellular matrix [(41)].

Lipid deposits result from increased endothelial permeability allowing small lipoproteins, such as LDL-c, to pass into the subendothelial space, where they become trapped by an extracellular matrix rich in proteoglycans [(42,43)]. These lipid deposits (identified as ApoB in immunohistochemistry) predominantly accumulate in the subendothelial regions of the fibrosa and at the base of the cusps, in contrast to healthy control valves [(42)]. This accumulation is subsequently followed by oxidation, triggered by oxygen-derived free radicals, resulting in the formation of oxidized LDL (Ox-LDL) and oxidized phospholipids (Ox-PL) [(44,45)].

Oxidized LDL particles play a central role in triggering inflammatory responses by recruiting and activating inflammatory cells such as macrophages, T lymphocytes, and mast cells. Ox-LDL particles interact with endothelial cells and macrophages, leading to an increased expression of

leukocyte adhesion molecules (e.g., VCAM-1, ICAM-1, and E-selectin), which enhances cellular recruitment and inflammation [2,46,47]. Ox-LDL particles are also cytotoxic, being phagocytized through scavenger receptors and subsequently accumulating in macrophages, ultimately resulting in the formation of foam cells [48]. Upon uptake of Ox-LDL, macrophages become activated and initiate a Th1 immune response, releasing pro-inflammatory cytokines (TNF, IL-1β, IL-2, IL-6, IFN-γ) [49]. The recruitment and activation of inflammatory cells promote extracellular remodeling via proteolytic enzymes, leading to tissue fibrosis and progressive calcification. Excessive Ox-LDL deposits also stimulate osteogenic differentiation of valvular interstitial cells (VICs) through toll-like receptors (TLR 2 and TLR 4), with Ox-LDL levels correlating with the severity of fibrocalcific remodeling of the valve [50,51].

Ox-LDL particles can be degraded by autotaxin (a circulating phospholipase produced by VICs) into lysophosphatidic acid (LPA), which further enhances the expression of leukocyte adhesion molecules and promotes VIC calcification via the nuclear factor-kappa B (NF-kB) and bone morphogenetic protein (BMP) signaling pathways [52].

Oxidized phospholipids, derived from Ox-LDL and LPA, are converted by lipoprotein-associated phospholipase A_2 (Lp-PLA_2) (produced by tissue macrophages) into lysophosphatidylcholine (LPC). LPC acts as a pro-inflammatory agent and indirectly promotes calcification through the protein kinase A (PKA) pathway and mitochondrial-induced apoptosis of VICs. Higher concentrations of Lp-PLA_2 are observed in tissues affected by aortic valve stenosis compared to healthy valves [53,54].

Following inflammation-driven remodeling of the extracellular matrix, the **propagation phase** is histologically characterized by increased fibrosis and calcification processes.

Valve fibrosis, alongside with calcification, contributes significantly to valve stiffening. Multiple studies have highlighted the importance of fibrosis, which may even surpass calcification in some population groups. For example, in female and younger patients, the predominance of fibrosis may explain discrepancies between hemodynamics (disease severity assessed by echocardiography) and the calcification load (as assessed by CTscan) [55]. Although the pathophysiological reasons are not fully understood, some studies suggest the increased production of extracellular matrix proteins, such as proteoglycans and tenascin-C, as well as the dysregulation of proteins involved in extracellular protein turnover, including Klotho and plasminogen activator inhibitor 1 (PAI-1) [56-58].

The renin-angiotensin system (RAAS) also appears to play a role in valvular fibrosis and inflammation via the action performed by angiotensin II on the AT1 receptor. In this regard, several factors are relevant: increased angiotensin-converting enzyme (ACE) levels are found in calcified aortic valves [59] , and there is a downregulation of the AT2 receptor, known for its anti-fibrotic and anti-inflammatory effects [60]. Furthermore, a systemic upregulation of the RAAS is also associated with hypertension, increasing afterload and mechanical stress on valve leaflets, exacerbating endothelial dysfunction and furthering valvular calcification [61].

Valve calcification occurs when VICs undergo a phenotypic shift toward myofibroblast-like and osteoblast-like cells, disrupting local calcium homeostasis. This shift promotes valvular calcification through the increased expression of pro-calcific factors (alpha-SMA, Vimentin, ALP, Runx2, Osteocalcin, Osteopontin, TGF-b, BMP 2, BMP 4, BMP 7, RANKL, Wnt/beta-catenin, ENPP1, MMP-10, etc.) and decreased expression of anti-calcific factors (FGF-2, fetuin-A, MGP, OPG, Notch 1, etc.) [36,61-68]. Although initially

triggered by the inflammatory response, the disruption of calcification signaling pathways gradually becomes the primary driver of extracellular matrix calcification [(69)].

Calcium dystrophy is another primary driver of calcification, marked by the precipitation of calcium- and phosphate-rich extracellular vesicles. These vesicles arise mainly from two sources: those secreted by macrophages and VICs, and apoptotic bodies from inflammation-damaged VICs. The deposits subsequently organize into hydroxyapatite molecules, which, upon contact with the extracellular matrix, form microcalcifications. At this stage, hydroxyapatite serves as an anchor for additional calcium vesicles, thereby exacerbating calcification and the inflammatory response. The resulting thickening of the valve increases hemodynamic stress and endothelial damage, creating a vicious cycle that drives a progressive snowball effect of calcification [(36,70,71)].

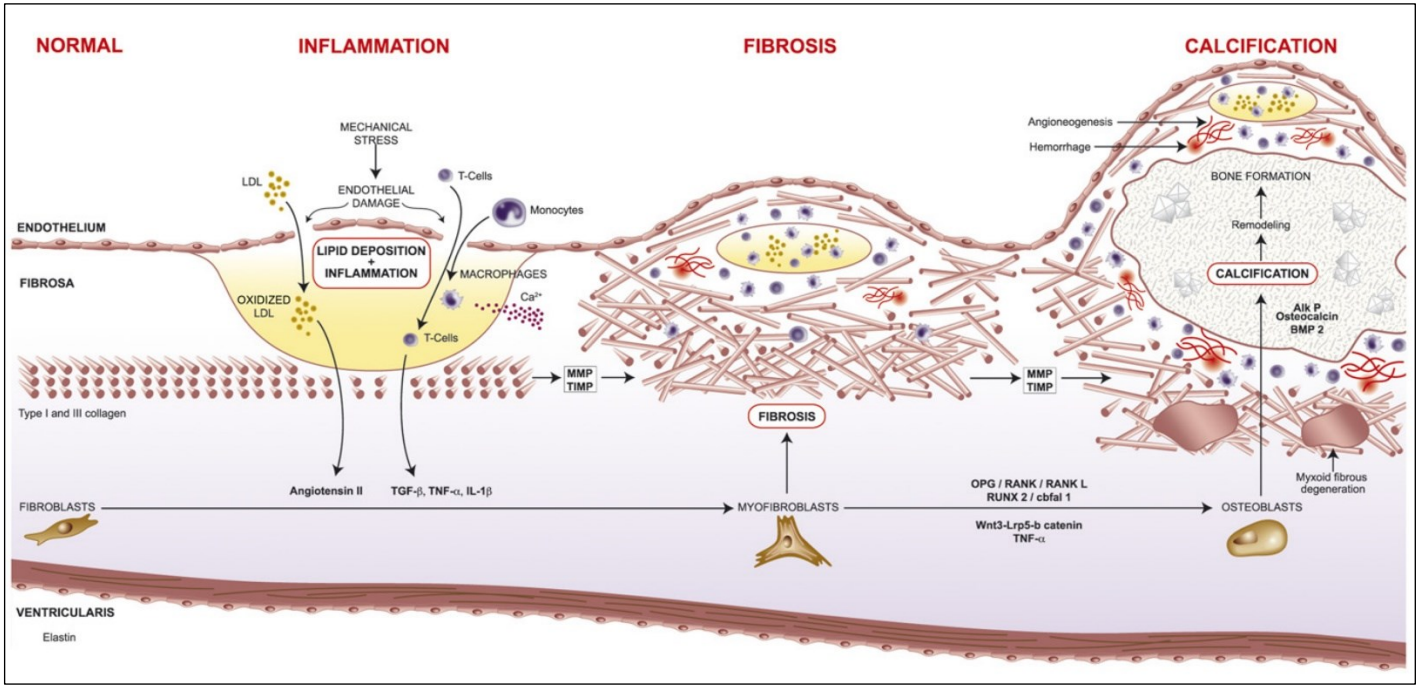


Figure 7: *Summary of the pathological processes operating within the valve in aortic stenosis. Adapted from Dweck et al, JACC, 2012 (46).*

Despite the numerous pathophysiological similarities with vascular atherosclerosis, including shared risk factors, aortic stenosis differs in its cellular control mechanisms. Specifically, inflammation and lipid deposits appear to play a key role in the initiation of the disease; however, the processes of calcification later predominate, becoming the main driver of progression to valve stenosis [61,72]. The self-sustaining nature of these mechanisms explains why most patients eventually progress to a severe form of the disease over time [73] (**Figure 8**).

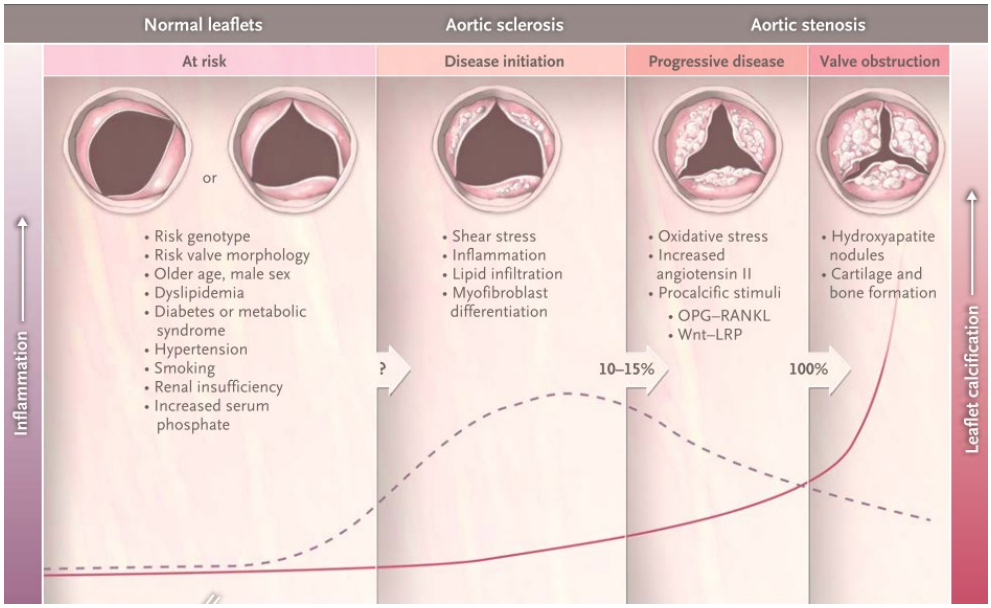


Figure 8: Association between clinical risk factors, mechanism of disease, and age of the patient. Inflammatory initial phase (dashed line) and calcific propagation phase (red line). Adapted from Otto CM et al. N Engl J Med 2014;371:44–756 [73].

2.2.5. Pathogenesis: the metabolic perspective

Aortic stenosis pathogenesis is driven by inflammation and calcification. Positron emission tomography (PET), unlike conventional methods, allows for molecular-level visualization in small structures such as heart valves when an appropriate tracer is available. In the case of aortic stenosis, studies primarily utilize two PET/CT tracers of interest: **18F-FDG** and **18F-NaF**:

- **18F-Fluorodeoxyglucose (18F-FDG)** is a glucose analogue taken up by cells via glucose transport proteins and incorporated into the glycolytic pathway. After phosphorylation by hexokinase, 18F-FDG-6-phosphate cannot undergo further metabolism, resulting in its intracellular trapping, particularly in cells with high metabolic demands, such as macrophages [(74)]. PET imaging using 18F-FDG has become a well-established method for quantifying vascular inflammation. However, its application for valvular assessment remains limited, except in cases of suspected endocarditis.
- **18F-Sodium fluoride (18FNaF)** is a bone-seeking tracer that binds to exposed calcium deposits through an ion exchange with hydroxyl groups on hydroxyapatite crystals, leading to fluorapatite formation [(75)]. Studies combining autoradiography and immunohistochemistry demonstrated a good correlation between 18F-NaF uptake and alkaline phosphate ($r = 0.65$; $P = 0.04$) a marker of calcification activity as well as osteocalcin staining ($r = 0.68$; $P = 0.03$), a well-recognized osteogenic protein which binds to hydroxyapatite [(15)]. Both CT scanning and 18F-NaF PET indicate the presence of calcium. However, the strength of 18F-NaF lies in its ability to preferentially bind areas with developing microcalcifications (<50µm) that precede macrocalcifications, which are the only ones detectable by CT (200-500µm). 18F-NaF uptake therefore provides a readout of calcification activity in aortic stenosis predicting where subsequent macroscopic deposits will be visible on CT (see Part 2.2.9.5).

The paradigm, in which inflammation leads to calcification, is supported by molecular imaging studies. These studies show that patients with baseline 18F-FDG PET/CT signals have a higher risk of developing visible calcifications on CT scan during follow-up compared to those without such signals [76,77]. Moreover, Dweck et al. explored the relative contribution of calcification processes and inflammatory activity in AVS in vivo using 18FNaF and 18F-FDG, respectively [74]. They demonstrated that calcification outweighed inflammation, particularly in the final disease stages, and showed a correlation between tracer uptake and calcific AV disease severity (**Figure 9**). 18F-NaF uptake was increased in sclerotic or stenotic valves and correlated with AS severity compared to age-, sex-, and comorbidity-matched healthy subjects ($r = 0.73$; $P < 0.001$). From a pathophysiological perspective, hemodynamic stress is usually maximal at the leaflet tips and the junctions with the aorta where the flexion occurs. Recurrent mechanical stress, combined with high shear forces and pressures, leads to valve calcification, which in turn further increases mechanical stress. 18F-NaF PET/CT showed a preferential tracer uptake in areas exposed to increased mechanical stress, hereby confirming its key role in the pathological process.

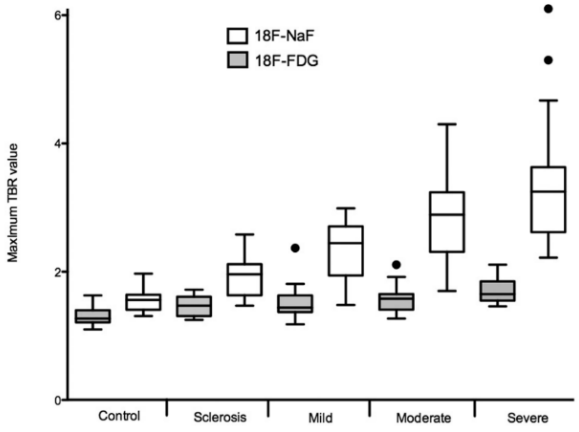


Figure 9: Uptake of 18F-FDG and 18F-NaF according to AS severity. The box plots illustrate the median and interquartile ranges of tissue-to-background ratios (TBR) for 18F-NaF (white boxes) and 18F-FDG (gray boxes). From Dweck et al. Circulation 2012;125:76-86 [74].

2.2.6. Pathophysiology: the hemodynamic perspective

Aortic stenosis constitutes an obstruction to left ventricular outflow, resulting in prolonged systolic ejection time and an increased systolic pressure necessary to sustain a constant cardiac output. Consequently, aortic stenosis imposes an elevated afterload on the left ventricle. Afterload is defined as the wall stress (σ) that opposes myocardial contraction. According to Laplace's law, this wall stress is proportional to the pressure (P) within the cavity, multiplied by its radius (r), and divided by twice the wall thickness (h) (**Figure 10**). In response to chronically elevated wall stress, the left ventricle undergoes adaptive changes to normalize this strain, resulting in concentric hypertrophy through the parallel addition of sarcomeric units (**Figure 11**), thereby increasing wall thickness (↑ h).

The Laplace's Law: $$\sigma = \frac{P * r}{2h}$$

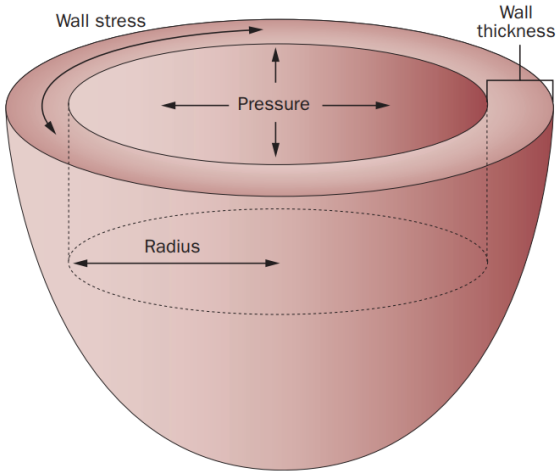


Figure 10: According to Laplace's Law, wall stress correlates with cavity pressure and radius, yet correlates inversely with wall thickness. Adapted from Gjesdal et al. Nature Reviews Cardiology 2011;8:673-685 [(78)].

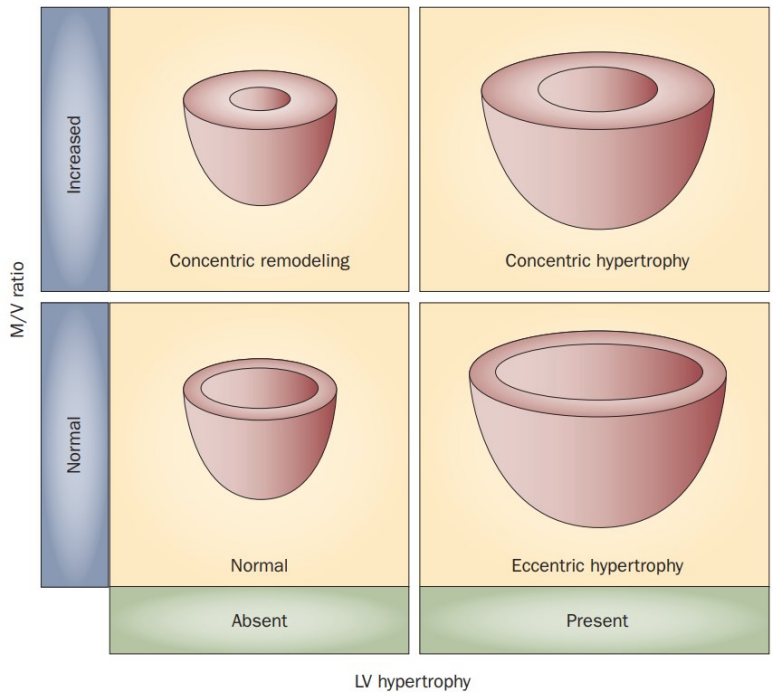


Figure 11: The patterns of cardiac remodeling. The parallel replication of sarcomeres in AS leads to concentric hypertrophy (normal cavity size) or concentric remodeling (decreased cavity size). Adapted from Gjesdal et al. Nature Reviews Cardiology 2011;8:673-685 [(78)].

For an extended period, the gradual increase in wall stress is compensated by ventricular remodeling, which maintains a balanced relationship between inotropy and afterload so as to preserve cardiac output. However, left ventricular hypertrophy can progressively become maladaptive, thereby leading to elevated left ventricular end-diastolic pressures and ultimately diastolic dysfunction. This stage is also characterized by the development of myocardial fibrosis and an increased risk of ischemia due to reduced coronary reserve and elevated oxygen demand. Once compensatory mechanisms (including remodeling, preload, and inotropy) are exhausted, further increases in afterload result in decreased stroke volume, initially during exertion and eventually at rest, a condition referred to as "afterload

mismatch". In the pressure-volume loop (**Figure 12**), there is a progressive loss of the ability to shift further to the right, accompanied by increased end-diastolic and end-systolic pressures. The pressure-volume product (external work) remains constant at maximum capacity, leading to a decline in stroke volume, which indicates the onset of systolic dysfunction.

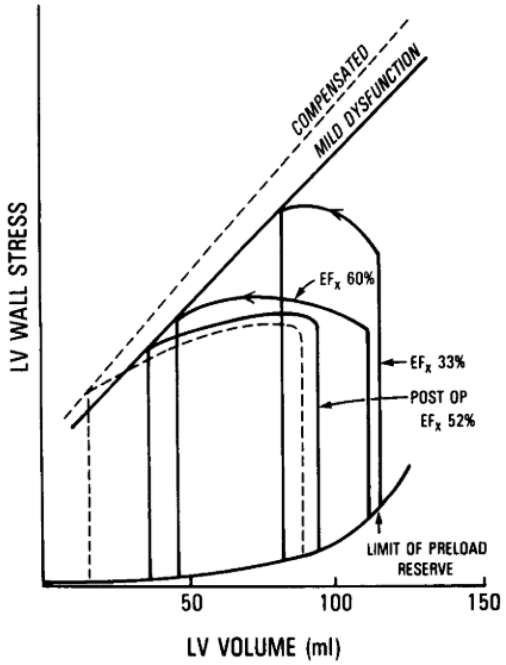


Figure 12: Pressure-volume loop in aortic stenosis. The curves represent the different phases of ventricular function, from compensated states to progressive dysfunction. Adapted from Ross et al, JACC, 1985 [(79)].

2.2.7. Natural history

The natural history of aortic stenosis has classically been characterized by a prolonged asymptomatic period due to the slow pathophysiological progression of the disease. This asymptomatic phase is associated with low morbidity and mortality over decades.

The rate of the disease's progression is influenced by the previously discussed risk factors and, therefore, varies from one patient to another. Willner et al. published a systematic review and meta-analysis of 24 prospective studies, including 5450 patients with mild to severe AS, and evaluated the mean annualized rates of AS progression based on hemodynamic and anatomical indices. They ultimately revealed an average increase in peak velocities of 0.2 m/s per year along with a decrease in valve opening area of 0.08 cm^2 per year. Populations with greater baseline AS severity were associated with more rapid AS progression [(80)].

Symptom onset typically coincides with the emergence of severe left ventricular obstruction but may occur earlier in the presence of comorbidities or multifactorial ventricular dysfunction. In 1968, Ross and Braunwald published their concept of this extended asymptomatic phase, followed by a rapid decline in survival once patients become symptomatic [(3)]. They reported average survival rates of 60 months in the presence of angina, 36 months with syncope, and 24 months in cases of heart failure (**Figure 13**). However, these findings were based on postmortem analyses, which accounts for the absence of surviving patients. Additionally, patients were younger at symptom onset than they are today, due to etiologies that were not exclusively degenerative.

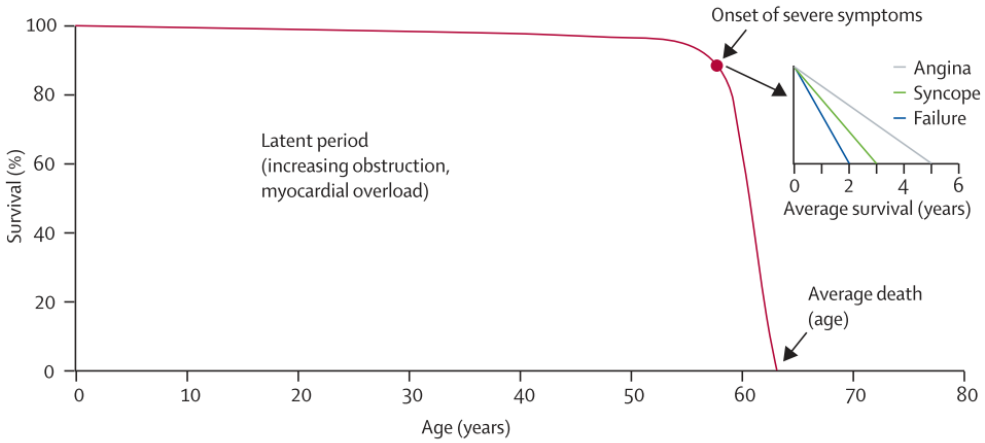


Figure 13: Representation of natural history in AS based on post-mortem data, emphasizing the long asymptomatic period precluding poor rate of survival once symptoms appear. Adapted from Ross and Braunwald Circulation. 1968;38:61-7 [(3)].

Symptom onset is therefore considered a critical point in the disease's natural history, as it marks the beginning of significantly increased mid-term mortality. However, in a more recent study, Rosenhek et al. (2010) demonstrated that even in asymptomatic patients with very severe aortic stenosis, event-free survival declines as the severity of the obstruction increases. The higher the peak transvalvular velocity, the worse the prognosis and the greater the likelihood of severe symptom onset [(81)].

2.2.8. Clinical presentation

As discussed in the previous section, the onset of symptoms attributable to aortic stenosis is of major importance and must be systematically assessed. The evaluation must therefore carefully differentiate between potential confounding pathologies that may present with similar clinical symptoms.

Dyspnea is typically the most common symptom in severe AS and can be explained by pulmonary congestion secondary to elevated left ventricular filling pressures. Symptom severity is classified according to the New York Heart Association (NYHA) scale, which is based on the degree of functional limitations in daily life (**Table 1**).

Table 1: New York Heart Association functional classification.

CLASS	DESCRIPTION OF PATIENT SYMPTOMS
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, or dyspnea. Comfortable at rest.
III	Marked limitation of physical activity. Less than ordinary activity causes fatigue, palpitation, or dyspnea. Comfortable at rest.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest.

Additionally, patients may experience episodes of syncope, which occur due to cerebral hypoperfusion caused by a decrease in stroke volume, typically observed with sudden reductions in LV preload or arrhythmias.

Angina is another potential symptom that can result from LV ischemia induced by higher oxygen consumption due to ventricular hypertrophy, decreased capillary density, reduced coronary perfusion gradient, and a frequent association with coronary artery disease in patients with aortic stenosis (41-60%) [(82)].

Finally, sudden cardiac death may also result as a manifestation of severe disease. Although this is more common in symptomatic patients, the risk is nevertheless estimated at 1% per year in asymptomatic patients [83].

Cardiac auscultation during a routine physical examination often serves as the starting point for an in-depth evaluation of potential valvular disease. In aortic stenosis, a holosystolic, crescendo-decrescendo murmur can be heard in the right second intercostal space. The murmur is generally harsh and radiates toward the carotid arteries, reflecting the turbulence caused by blood flowing through the narrowed valve. The intensity of the murmur typically increases with the severity of the stenosis, resulting in higher transvalvular velocities (and therefore increased blood flow turbulence), except in patients with reduced cardiac output. Both the time to reach peak intensity and the overall duration of the murmur generally increase with the severity of the disease. Abnormalities in the second heart sound (S2) are also important in the identification of cases of aortic stenosis. Prolonged systolic ejection time often results in a paradoxical splitting of S2, where the aortic component follows the pulmonary valve closure sound. When the motion of the valve leaflets is severely restricted, a reduction or even complete absence of S2 may be observed (**Figure 14**).

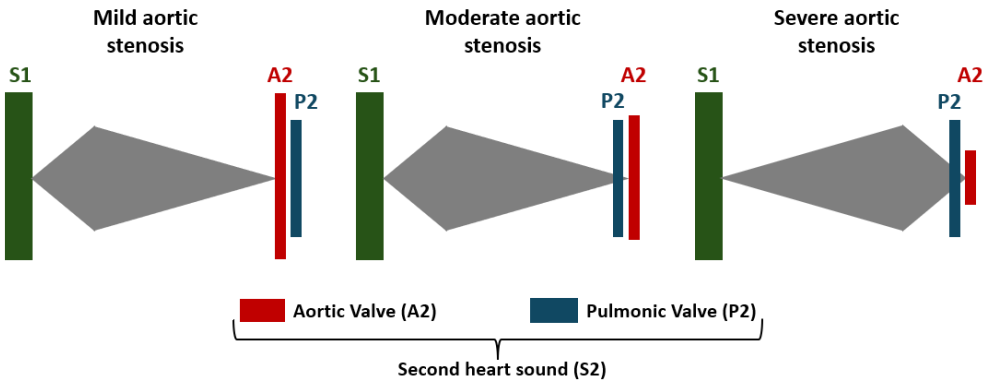


Figure 14: Murmur of aortic stenosis.

On palpation, a systolic thrill may be felt in the right second intercostal space when the murmur is of high intensity. In patients with severe aortic stenosis, the carotid pulse may be weak and delayed ("parvus et tardus" pulse); however, this sign may be absent in cases of significant carotid artery stiffness.

Although all these clinical signs are associated with the presence of severe aortic stenosis, none are both sensitive and specific to the disease. Therefore, a comprehensive evaluation utilizing multimodal imaging is essential if any of these suggestive signs are present.

2.2.9. Diagnostic and imaging tools

The diagnosis of aortic stenosis, along with the assessment of its severity and progression over time, requires the use of imaging techniques. Specifically, echocardiography is the primary examination used for this purpose, although it has certain limitations that necessitate the use of additional techniques, such as CT scans or cardiac MRI. As a result, hemodynamic assessment of the disease's severity through left heart catheterization is now used far less frequently due to its significantly more invasive nature compared to other modalities.

2.2.9.1. Echocardiography

Transthoracic echocardiography is currently recognized as the gold standard for diagnosing and assessing the severity of AS, owing to its accessibility and cost-effectiveness. It allows for a visual assessment of the number of valve leaflets, a semi-quantitative evaluation of any calcification, and a hemodynamic severity assessment through Doppler measurements. Beyond the valve itself, the exam also provides a comprehensive evaluation of the overall impact of chronic afterload increase on the heart, including assessments of left ventricular morphology and function, left atrial volume, pulmonary pressures, and right ventricular function.

Standard measurements

The hemodynamic assessment of AS severity is based on the measurement of three main parameters: peak transvalvular velocity, mean transaortic gradient, and aortic valve opening area. These three parameters are intrinsically linked by the law of energy conservation: as the aortic valve area decreases, velocities increase, and potential energy is lost. Consequently, the transvalvular pressure gradient increases in parallel.

The **peak jet velocity** is measured using continuous-wave (CW) Doppler across multiple acoustic windows, including apical, right parasternal, and suprasternal views. This measurement is straightforward as it does not require mathematical assumptions; however, it must be performed accurately. In light of this, the transducer should be carefully positioned parallel to the blood flow (at a 0° angle) since any angulation will result in a slight underestimation of the true velocities. However, the degree of underestimation is 5% or less if the intercept angle is within 15° [(17)]. Angle correction is not recommended, as it may exacerbate or increase the risk or presence of errors due to the jet's unpredictable direction. Moreover, the waveform envelope provides valuable information about the severity of valvular obstruction, as indicated by the peak velocity, as well as the extended systolic ejection time and delay from valve opening to peak velocity (**Figure 15**).

The **velocity time integral** (VTI) is the area under the spectral curve, representing the sum of all velocities recorded over the systolic period. It is used to calculate parameters such as stroke volume (SV) and aortic valve area (AVA).

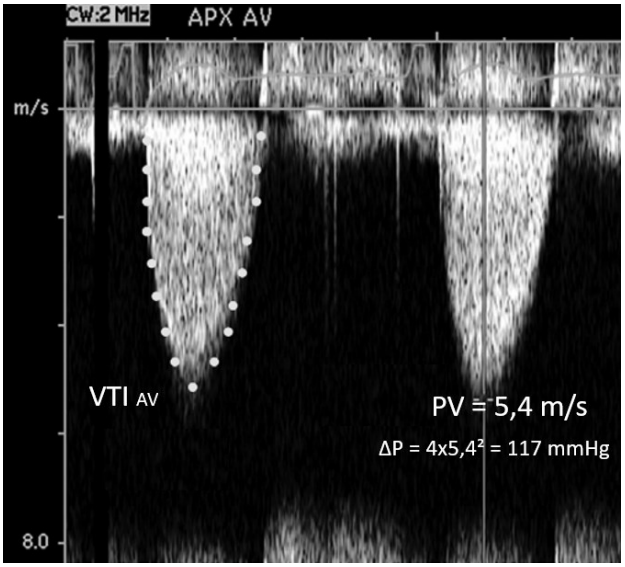


Figure 15: Continuous-wave Doppler recording of a maximum jet velocity (PV) of 5.4 m/s in AS. VTI AV= velocity time integral through the aortic valve. Adapted from Baumgartner et al. J Am Soc Echocardiogr 2009;22:1-23; quiz 101-2 [(17)].

The **maximum pressure gradient** between the left ventricular outflow tract and the ascending aorta is estimated using the simplified Bernoulli equation, based on the principle of energy conservation:

Simplified Bernoulli equation: $\Delta \mathbf{Pmax} = \mathbf{P1} - \mathbf{P2} = \mathbf{4V^2max}$

where P1 is the upstream pressure and P2 is the downstream pressure; V is the peak velocity measured between the two chambers.

As demonstrated above, gradients are derived from velocity measurements; thus, the peak gradient, calculated from peak velocity, provides no additional information. The **mean gradient** is the average of all instantaneous gradient measurements across the valve during systole. It is generated automatically by current echocardiographic systems on the VTI curve (**Figure 15**). The peak and mean gradients are generally well correlated but depend on the shape of the velocity curve, which varies with the severity

of stenosis and flow rate. Measuring the mean gradient, therefore, provides the clinician with additional information.

The **aortic valve area** (AVA) is calculated using the continuity equation (**Figure 16**), based on the law of mass conservation. This principle states that the stroke volume passing through the left ventricular outflow tract is equal to the stroke volume flowing across the aortic valve, as expressed in the following equation:

$$\mathbf{AVA\ X\ VTI}_{\mathbf{AV}} = \mathbf{CSA}_{\ \mathbf{LVOT}}\ \mathbf{X\ VTI}_{\mathbf{LVOT}}$$

where CSA LVOT is the LV outflow track cross-sectional area; VTI is velocity time integral in the LVOT or in aortic valve (AV).

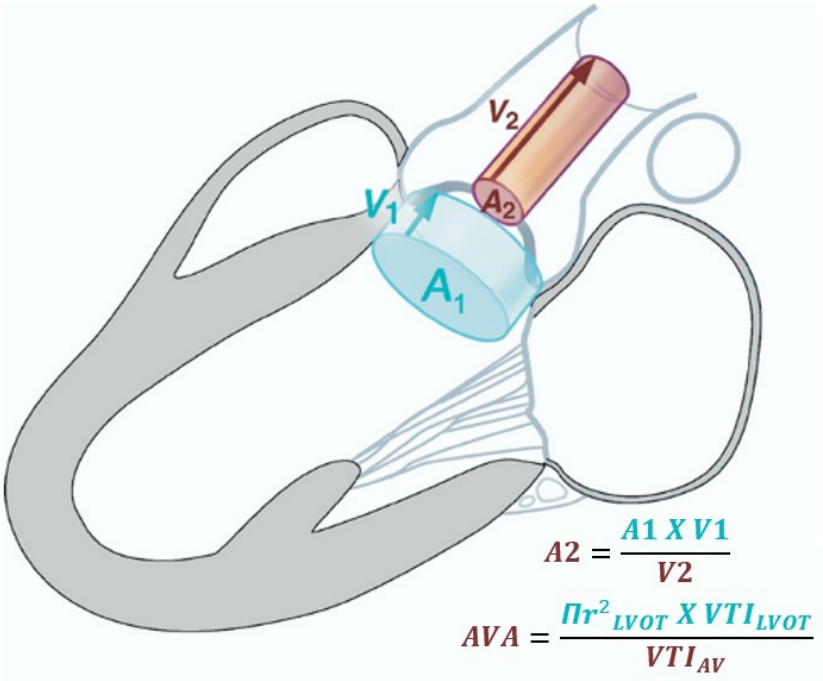


Figure 16: Continuity equation for aortic valve area calculation. Adapted from Baumgartner et al. J Am Soc Echocardiogr 2009;22:1-23; quiz 101-2 [17].

The continuity equation is widely used in clinical practice, however there are several considerations that are necessary. Specifically, it is essential to understand that the calculated orifice area depends on the maximum velocities reached at the narrowest point, i.e. the "vena contracta" [84]. Therefore, the area obtained corresponds to the effective orifice area (EOA) rather than the geometric area (GOA), as the effective area forms downstream of the valve due to the convergence of streamlines (**Figure 17**). The differences between effective and geometric aortic valve areas and their clinical implications will be discussed further in Part 3.

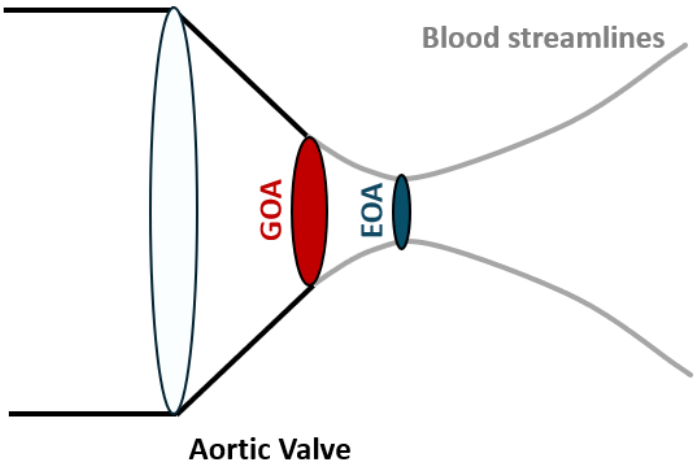


Figure 17: Definition of effective orifice area (EOA) and geometric orifice area (GOA).

To solve the continuity equation and obtain an accurate calculation of the AVA, precise measurement of the LVOT diameter is essential, as any approximation is squared, resulting in significant inaccuracy. This measurement should generally be taken 0.5 to 1 cm upstream from the valve annulus to ensure laminar flow during the VTI measurement without spectral dispersion [17]. The diameter is measured mid-systole, aligning the

two inner edges between the septum and the anterior mitral leaflet (**Figure 18**).

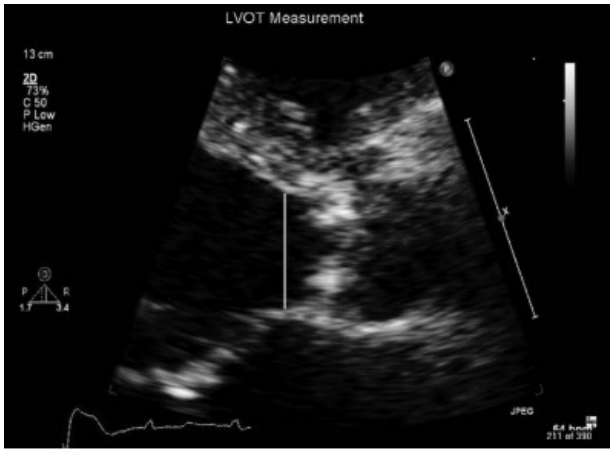


Figure 18: LVOT diameter measured in the parasternal long-axis view. Adapted from Baumgartner et al. J Am Soc Echocardiogr 2009;22:1-23; quiz 101-2 [(17)].

Furthermore, the continuity equation assumes a circular shape for the LVOT, rather than its actual elliptical shape. Consequently, this assumption leads to a systematic and significant underestimation of the stroke volume and AVA compared to any measurements obtained with computed tomography [(85-87)] or cardiac magnetic resonance [(88)].

It is also possible to utilize aortic valve planimetry using 2D or 3D transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) to measure the anatomical (geometric) opening area (GOA). However, this method is not preferred due to its tendency to overestimate the actual valve area as it does not rely on flow measurement. Moreover, extensive calcification can produce echogenic artifacts that hinder the clear visualization of the valve edges. Nevertheless, this technique may be justified in cases of low cardiac output, where any Doppler-based estimation of the effective orifice area (EOA) is reliable.

Integrated parameters

New parameters and concepts have been developed in order to address the inherent limitations of the basic echocardiographic measurements discussed previously. Although these parameters have been designed to reduce the potential for any error to arise from the strict assumptions of formulas and to minimize flow dependency, they still remain underutilized in routine practice.

Dimensionless Velocity Index (DVI)

To address errors associated with measuring the size of the left ventricular outflow tract, a primary source of error in the continuity equation, this new parameter has been proposed [5]. This parameter is effectively a ratio of the LVOT and aortic valve (AV) velocity time integrals (VTIs), representing a modified, unitless version of the continuity equation.

$$\mathbf{DVI} = \frac{\mathbf{VTI_{LVOT}}}{\mathbf{VTI_{AV}}}$$

A DVI value <0.25 is highly likely to be associated with severe AS [89].

Pressure Recovery (PR)

This phenomenon relates to the law of energy conservation: as blood flows through the vena contracta, its kinetic energy reaches a maximum while its potential energy is at a minimum. Subsequently, the flow decelerates, leading to energy loss through turbulence formation. The reduction in velocity allows for an increase in static pressure, peaking at the point where the flow reattaches (linearly). This reconversion of kinetic energy into potential energy is referred to as pressure recovery [90,91]. Consequently, the pressure gradient between the LVOT and the vena contracta (maximum TPG) is greater than the gradient between the LVOT and the aorta (net TPG) (**Figure 19**).

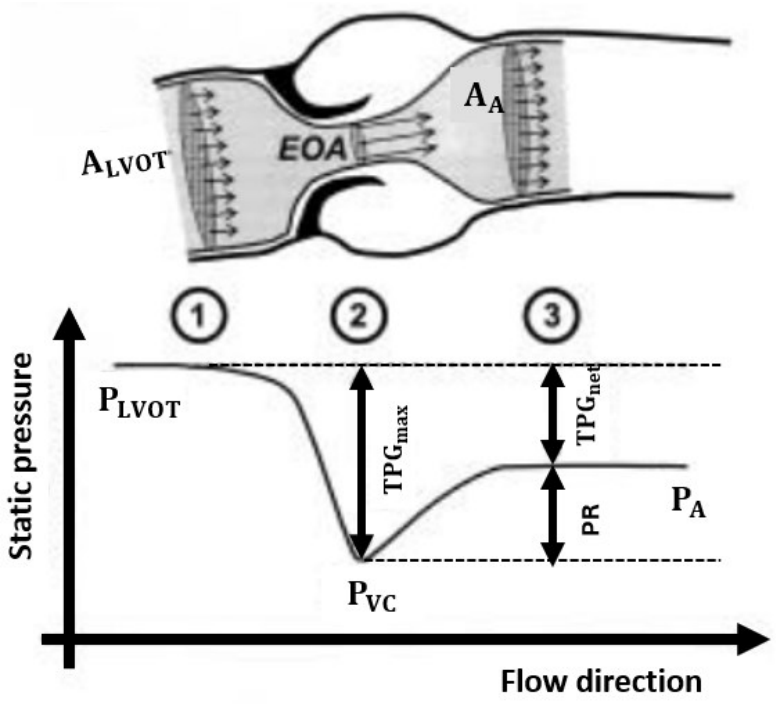


Figure 19: Systolic flow through an aortic stenosis. Normal flow with high static energy in the LVOT (1), maximal kinetic energy through the vena contracta and minimal potential energy (2), pressure recovery (PR) in the aorta (3). AA: Aortic cross-sectional area; ALVOT: LVOT cross-sectional area; EOA: effective orifice area; PA: Aortic pressure; PLVOT: LVOT pressure; PVC: Pressure at the vena contracta; TPGmax: Maximal transvalvular pressure gradient (=PLVOT-PVC); TPGnet: Net transvalvular pressure gradient (=PLVOT-PA). Adapted from Garcia et al. J Heart Valve Dis 2006;15:601-8 [(90)].

Pressure recovery is more pronounced for a given degree of valvular obstruction when the cross-sectional area of the ascending aorta is smaller (sino-tubular junction < 30mm). Doppler echocardiography, which calculates the pressure gradient based on peak velocities alone, therefore tends to overestimate stenosis severity resulting in a smaller calculated AVA, compared to measurements obtained by left heart catheterization [(90,92)]. The

latter technique assesses the pressure gradient between the LVOT and the aorta, which is distal to the vena contracta, thereby accounting for pressure recovery (net TPG).

The proposed formula for calculation is as follows, and is expressed in mmHg [92]:

$$\textbf{Pressure recovery} = \textbf{2 X PG X } \frac{\textbf{EOA}}{\textbf{AA}} \textbf{ X } (\textbf{1} - \frac{\textbf{EOA}}{\textbf{AA}})$$

where AA is the cross-sectional area of the ascending aorta.

Energy Loss Index (ELI)

To assess aortic stenosis severity, incorporating pressure recovery is valuable, especially in cases with a small ascending aorta cross-sectional area or discordance among traditional severity parameters. The energy dissipation from flow deceleration correlates with increased left ventricular afterload, making this parameter the most closely associated with aortic stenosis severity. Its formula accounts for pressure recovery and is typically indexed to body surface area, offering a more accurate representation of ventricular load than either the EOA or GOA [90,93]:

$$\textbf{Energy loss index} = \frac{\textbf{EOA X AA}}{\textbf{AA} - \textbf{EOA}} \textbf{ X } \frac{\textbf{1}}{\textbf{BSA}}$$

where AA is the cross-sectional area of the ascending aorta and BSA represents the body surface area.

Left Ventricular Stroke Work Loss (LVSWL)

This parameter represents the fraction of ventricular work (pressure × volume) lost with each systole as the blood crosses the aortic valve. It is expressed as a percentage of total systolic work. When a mean transvalvular gradient results in a loss of more than 25% of the total end-systolic pressure generated by the left ventricle (mean gradient + systolic arterial pressure), this parameter is indicative of severe stenosis [94].

$$\textbf{Left ventricular stroke work loss} = \frac{\textbf{MG}}{\textbf{MG} + \textbf{SAP}} \textbf{ X 100}$$

where MG is the mean transvalvular gradient, and SAP is systolic arterial pressure.

Stroke volume index (SVi)

Given that the majority of echocardiographic parameters are flow-dependent, calculating the ejected volume per heartbeat has become essential in the systematic assessment of aortic stenosis severity and is now a key parameter for evaluating AVA-MG discrepancies [4,5]. In order to account for variations in body size and ventricular volume, it is recommended to index this measurement to body surface area:

$$\textbf{Stroke volume index} = \frac{\textbf{CSA}_{\textbf{LVOT}} \textbf{ X VTI}_{\textbf{LVOT}}}{\textbf{BSA}}$$

where $\mathrm{CSA}_{\mathrm{LVOT}}$ is the LVOT cross-sectional area and $\mathrm{VTI}_{\mathrm{LVOT}}$, the velocity time integral through the LVOT.

Conventionally, a left ventricular stroke volume index <35 mL/m² defines low-flow status [95].

Flow rate (FR)

Stroke volume is often used as a surrogate for cardiac flow; however, it does not account for the concept of time in its calculation. By definition, flow is the volume per unit of time (ml/s):

$$\textbf{Flow rate} = \frac{\textbf{SV}}{\textbf{SET}}$$

where SV is stroke volume and SET is systolic ejection time.

Recently, flow rate has been proven to hold prognostic added value in patients with AVA <1cm², as it better predicts mortality when the mean gradient are < 40 mmHg [96].

Valvulo-arterial Impedance (Zva)

Valvulo-arterial impedance is a measure of global left ventricular afterload, integrating valvular obstruction and systolic arterial pressures, normalized by stroke volume index. Zva thus reflects the valvular and arterial factors opposing ventricular ejection by absorbing the mechanical energy generated by the left ventricle, and which serves as a strong independent predictor of survival in AS [95,97-99].

$$\mathbf{Zva} = \frac{\mathbf{SAP} + \mathbf{MG}}{\mathbf{SVi}}$$

where MG is the mean transvalvular gradient, SAP is systolic arterial pressure, and SVi is the stroke volume index.

Left Ventricular Wall Stress (LVWS)

Left ventricular wall stress is not a direct measure of aortic stenosis severity, but rather indicates the mechanical stress exerted on the ventricular walls. As discussed above, it is governed by Laplace's law and is directly influenced by LV pressure and cavity size, and is inversely related to LV wall thickness.

$$\mathbf{LVWS} = \frac{\mathbf{0.98\ X\ 0.334\ X\ SAP\ X\ ESD}}{\mathbf{PWT\ X}\left(\mathbf{1} + \left(\frac{\mathbf{PWT}}{\mathbf{ESD}}\right)\right) - \mathbf{2}}$$

where SAP is the systolic arterial pressure, ESD is the end-systolic diameter and PWT is the end-systolic posterior wall thickness.

Left ventricular Global Longitudinal Strain (GLS)

Global longitudinal strain (GLS) utilizes 2D speckle-tracking technology to track ventricular deformation throughout the cardiac cycle. Similar to left ventricular ejection fraction (LVEF), this parameter is load-dependent and influenced by afterload, which is elevated in aortic stenosis. Its clinical significance lies in its ability to detect subclinical LV dysfunction, making it a

superior and more reliable predictor of clinical events compared to LVEF [100,101].

$$\mathbf{GLS}\ (\%) = \frac{\mathbf{MLs} - \mathbf{MLd}}{\mathbf{MLd}}$$

where LM is myocardial length in systole (MLs) and in diastole (MLd). By definition, GLS is negative, as MLs is shorter than MLd. GLS is measured across three planes and then averaged.

2.2.9.2. Catheterization

Cardiac catheterization consists of measuring pressure in the left ventricle and at the level of the aortic root, downstream from the vena contracta, thereby allowing for the calculation of a peak-to-peak gradient. However, in practice simultaneous measurement of these two sources of pressure is not feasible, as the peak ventricular pressure does not occur concurrently with the peak aortic pressure [102]. Therefore, it is recommended to use the mean gradient, which is the area under the curve between the two peaks, to estimate the severity of aortic stenosis (**Figure 20**).

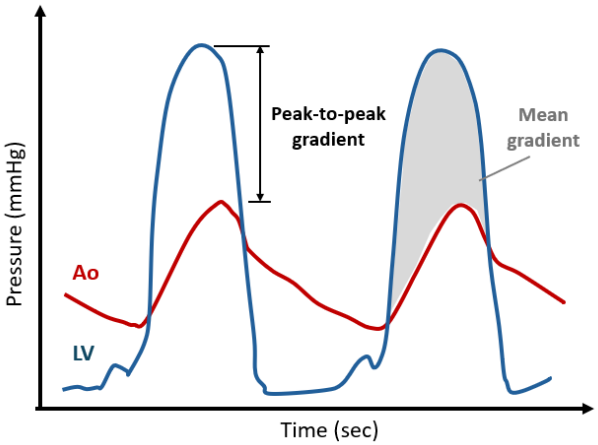


Figure 20: Peak-to-peak and mean gradient measurements in a patient with aortic stenosis.

Catheterization also enables the calculation of cardiac output—most commonly by thermodilution—although the Fick method can also be applied. Once the pressure gradient and cardiac output are known, the aortic valve area can be calculated using the Gorlin formula [103]:

$$\mathbf{AVA} = \frac{\mathbf{CO}}{\mathbf{44.3\ X\ HR\ X\ SEP\ X}\sqrt{\mathbf{MG}}}$$

where CO is for cardiac output, HR is for heart rate and SEP is for systolic ejection period.

The AVA calculated using the Gorlin formula provides an effective orifice area because it is based on the same hemodynamic principles as the Doppler-derived EOA and is, therefore, flow-dependent. However, the Gorlin-derived AVA differs from the Doppler EOA in two key ways. First, the Doppler EOA calculates a maximal pressure gradient (ΔP) at the vena contracta using the Bernoulli equation, while the catheter-derived AVA employs a net ΔP that accounts for pressure recovery. Second, the Gorlin formula introduces errors in its formulation by incorporating a constant intended to approximate the anatomic rather than the effective valve area [104]. As a result, the catheter-derived AVA is typically larger than the Doppler-derived EOA [90,104,105]. Currently, cardiac catheterization is not recommended when echocardiography has already confirmed the severity of aortic stenosis but may be utilized in cases where there is discordance between parameters [105].

2.2.9.3. Multidetector tomography

Cardiac CT is a valuable tool for assessing the severity of aortic stenosis, owing to its high spatial and temporal resolution. Its main advantage lies in its sensitivity in detecting calcium deposits on the valve leaflets and annulus (**Figure 21**). This imaging technique allows for the quantification of the calcific load on the aortic valve, which is directly correlated with stenosis

severity [106-108]. This quantification is typically performed using the Agatston score, with a calcification being defined as an attenuation of ≥ 130 HU with an area greater than 3 contiguous pixels [105]. A weighting factor is subsequently applied based on the maximum density. The Agatston score for each region is calculated by summing the density scores, which are multiplied by the area measured in each section.

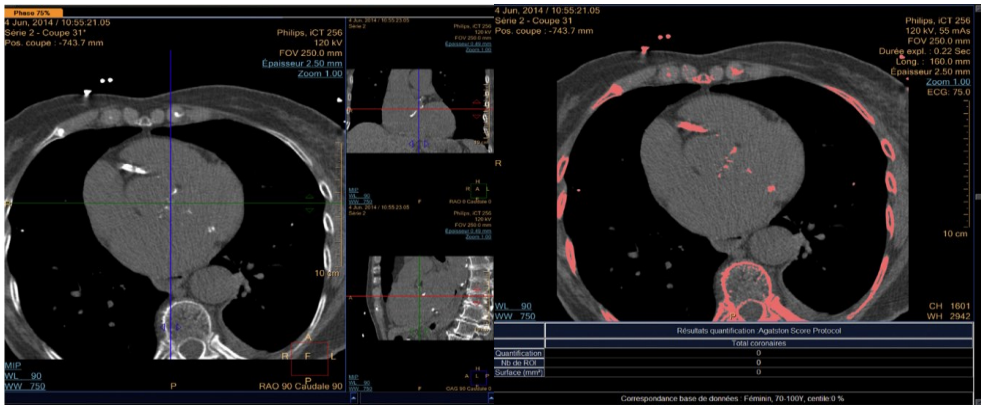


Figure 21: Aortic valve calcification assessment for calcium scoring (left panel) and image reconstruction and visualization in multiple planes (right panel). Adapted from Boulif et al. Front Cardiovasc Med 2021;8:673519 [109].

Calcification measurement offers a flow-independent assessment of stenosis severity, making it particularly useful in cases of significant systolic LV dysfunction or gradient-AVA discordance [4,5]. Due to differences in calcific load between men and women with similarly severe stenotic valves, current guidelines establish the following thresholds for assessing aortic stenosis severity:

Table 2: Likelihood of severe AS in males and females with AVC load.

Severe aortic stenosis likelihood	**Agatston units threshold**	
	Male	Female
Highly likely	3000	1600
Likely	2000	1200
Unlikely	1600	800

Boulif et al. have clarified the application of these AV calcification thresholds through their study of 57 explanted valves [109]. Beyond sex-related differences, it is essential to understand that these thresholds can be applied to bicuspid valves, provided that the data are normalized to the LVOT cross-sectional area. Additionally, since tube potential and slice thickness independently influence Agatston scores, clinicians should exercise caution when applying severity thresholds from the literature if the scanner settings in those studies differ from those employed in clinical practice.

Recently, Cartlidge et al. published a contrast-enhanced computed tomography study assessing the severity of aortic stenosis, including the role of valvular fibrosis in hemodynamic obstruction [110]. They evaluated the fibrocalcific volume (the combined indexed non-calcific and calcific volume) and compared it with peak aortic velocity. Compared to the Agatston score, fibrocalcific volume demonstrated a stronger correlation with peak aortic jet velocity than the Agatston score (r=0.59 for the Agatston score and r=0.67 for fibrocalcific volume), particularly in females (r=0.38 and r=0.72, respectively). The use of contrast agents in the evaluation of aortic stenosis may therefore provide clinicians with valuable insights for patient management in the future.

As discussed in the echocardiography section, CT imaging can also be used to measure the planimetry of the aortic valve, thereby providing a geometric orifice area. Finally, CT imaging is also used, with the aid of a contrast agent, to measure the annulus size and assess vascular accessibility prior to performing a percutaneous valve replacement.

2.2.9.4. Cardiac magnetic resonance

MRI serves as an additional tool in the evaluation of aortic valves. The development of cine sequences enables anatomical visualization of the valve as well as measurement of its opening area (GOA). Using phase-contrast sequences, hemodynamic measurements of velocities across the valve are

also possible (**Figure 22**) and closely correlate with TTE measurements [111,112]. These measurements allow for the calculation of an EOA using various methods, such as the Hakki formula derived from the Gorlin equation or a modified continuity equation [111,113].

Moreover, a key advantage of MRI lies in its ability to accurately measure ventricular volumes, masses, and function, as well as to characterize ventricular remodeling. Late gadolinium enhancement imaging allows the assessment and detection of focal fibrosis, which correlates directly with histology [114,115] and prognosis [116-118] (**Figure 23**). Additionally, extracellular volume (ECV) quantification [119] and changes in native T1 [120] over time are also important independent predictors of mortality in patients with severe AS, both before and after aortic valve replacement.

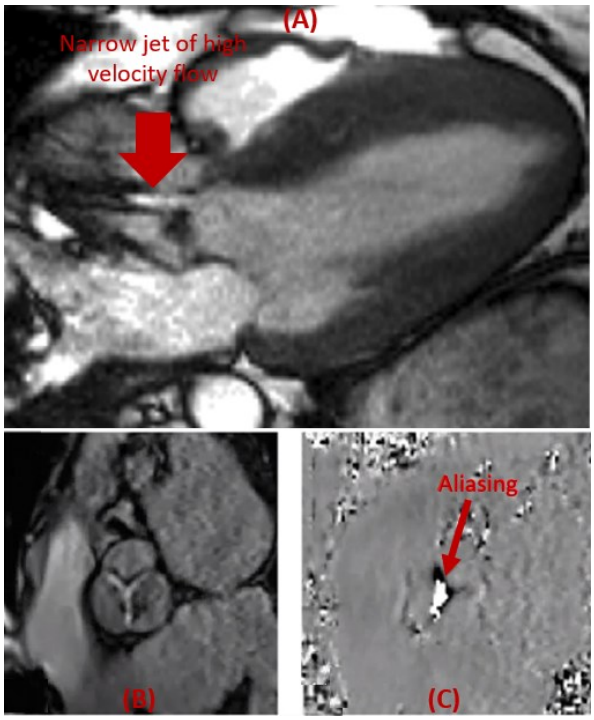


Figure 22: SSFP cine sequences of the aortic valve in three chambers (A) and short-axis (B) views. A 2D phase contrast sequence measures peak jet velocity with aliasing, suggesting higher velocities than 4 m/s (encoded velocity) (C). Adapted from The EACVI Textbook of Cardiovascular Magnetic Resonance. Oxford University Press, 2018 [121].

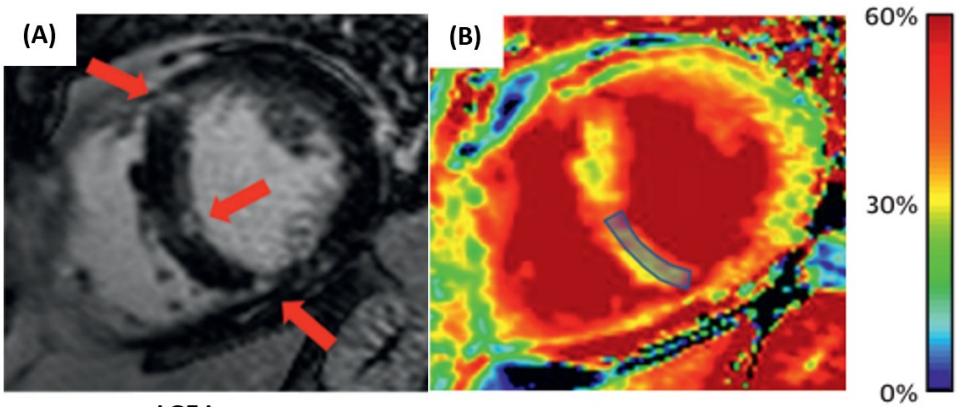


Figure 23: CMR short-axis images with late gadolinium enhancement (A, red arrows) and an extracellular volume map derived from T1 measurements in the septal wall (shaded blue area) and the blood pool (center of the LV cavity) (B). Adapted from Everett et al. J Am Coll Cardiol 2020;75:304-316 [(119)].

2.2.9.5. Positron emission tomography

PET/CT is a non-invasive imaging technique that enables visualization of ongoing molecular processes within small structures, such as the coronary arteries or heart valves. Currently, this imaging technique is not routinely used for assessing the severity of AS. However, it holds significant promises due to its ability to provide complementary information on disease activity. This capability could enable early disease detection, prediction of disease progression, and monitoring of preventive or therapeutic strategies.

Regarding AS, the most promising tracer is currently **18F-sodium fluoride (18F-NaF)**, as previously introduced, due to its high affinity for binding to microcalcifications. This tracer is the focus of intensive research in cardiovascular pathologies, particularly in native and prosthetic valvular diseases.

In native AS, 18F-NaF uptake provides a readout of calcification activity predicting where subsequent macroscopic deposits will be visible on CT [(15)].

When combining the results from both CT and PET, two interesting mismatch patterns may be observed between the modalities. The first mismatch pattern consists of PET positive areas without underlying CT calcifications, which is due to the greater binding capacity of 18F-NaF in sites with microcalcifications, whose nanocrystalline structure has a greater contact area with the tracer compared to macrocalcifications. Irkle et al. demonstrated that 18F-NaF binding is more pronounced in microcalcification sites than in large macroscopic deposits [122]. By contrast, the second mismatch pattern concerns dense calcium regions on CT with relatively faint or absent 18F-NaF uptake due to the relative inactivity of macrocalcifications whose hydroxyapatite core is internalized and hidden from the 18F-NaF tracer [15]. 18F-NaF uptake can, therefore, serve as a marker of intravalvular calcification activity, whereas the CT calcium score provides information about the overall amount of macrocalcification, whether quiescent or active.

Interestingly, prospective studies have shown that baseline 18F-NaF uptake is correlated with subsequent changes in AVC score after 2 years ($r = 0.8$; $P < 0.001$) [13,15]. Even at an early stage, i.e. aortic sclerosis, Nakamoto et al. showed that increased 18F-NaF uptake correlated with subsequent calcium score progression at 2 years [123] (**Figure 24**).

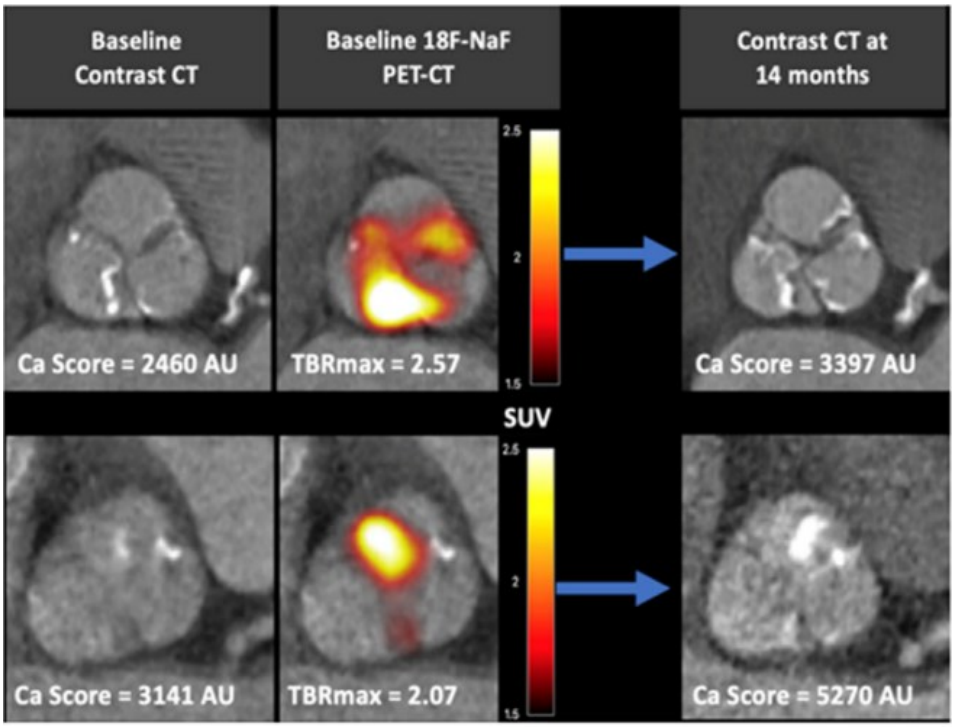


Figure 24: Prediction of calcium deposition in native aortic valves. Progressive aortic valve calcium score and new macroscopic calcium deposits in a similar distribution to that of baseline PET uptake. TBRmax: maximum aortic valve max tissue-to-background ratio, SUV: standard uptake value, PET: positron emission tomography; CT: computed tomography. From Fletcher et al. J Nucl Cardiol 28(2):481-491, 2021 [(124)].

Moreover, 18F-NaF activity can predict hemodynamic valve deterioration, yet with a moderate accuracy (mean gradient r = 0.32; 95% CI [0.13,0.50]; P = 0.001, and peak gradient (r = 0.32; 95% CI [0.12,0.49]; P = 0.002) [(60)]. In a 2-year prospective trial, 18F-NaF turned out to be an independent predictor of clinical outcome (composite of cardiovascular death and AV replacement) after adjustments for age and sex (HR: 1.55; 95% CI [1.33, 1.81]; P < 0.001) [(13)].

Finaly, 18F-NaF PET/CT emerges as an attractive endpoint for clinical studies aiming at understanding the pathophysiological processes underlying disease progression and at establishing the efficacy of potential new therapies. Furthermore, as changes in 18F-NaF uptake are likely to be detectable earlier than with other conventional techniques, like CT or echocardiography, that could require several years to demonstrate a potential treatment effect, 18F-NaF PET/CT arises as an excellent exploratory efficacy endpoint. Several clinical studies have investigated the impact of therapeutic interventions in AS using 18F-NaF uptake as an endpoint; however, none have demonstrated efficacy to date (**Table 3**).

Table 3: Studies Using 18F-NaF PET/CT for Monitoring Therapeutic Interventions in Valvular Heart Diseases.

Study	Target	Intervention	Population	Follow-up	Primary Endpoints
PCSK9 inhibitors in the progression of aortic stenosis [NCT03051360].	Apo B-containing lipoproteins; PCSK9.	Biweekly injection of PCSK9 inhibitor vs placebo.	Mild-moderate AVS (n = 140).	2 years	Change in CT-AVC score and 18F-NaF uptake (ongoing).
SALTIRE II - Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis [125].	Mineral metabolism.	Alendronic acid (n = 50) vs denosumab (n = 50) vs placebo injections (n=50).	AVS (Vmax >2.5 m/s).	2 years	No change in CT-AVC score between denosumab vs placebo or alendronic acid vs placebo. No differences in change in Vmax or 18Fsodium fluoride AV uptake between groups.
BASIK2 - Bicuspid Aortic Valve Stenosis and the Effect of vitamin K2 on Calcium metabolism on 18F-fluoride PET/MR [126].	Vitamin K2-matrixgla-protein.	Daily vitamin K2 at a dose of 360mg (n = 22) Vs placebo (n = 22).	Bicuspid aortic valve and calcified mild to moderate AVS.	18 months	Change in aortic valve 18F-fluoride uptake at 6 months; change in CT-AVC score at 6 and 18 months (ongoing).

AVS, aortic valve stenosis; 18F-NaF, 18F-sodium fluoride; PCSK9, proprotein convertase subtilisin/kexin type 9; Apo B, apolipoprotein B; AVC, aortic valve calcification; CT, computed tomography; Vmax, pic jet velocity.

2.2.10. Aortic stenosis grading

European and American guidelines for valvular heart disease propose a classification system for the severity of aortic stenosis using the following parameters:

Table 4: Classification of aortic stenosis severity. Adapted from Baumgartner et al. J Am Soc Echocardiogr 2009;22:1-23; quiz 101-2 [17].

	Aortic sclerosis	Mild stenosis	Moderate stenosis	Severe stenosis	Very severe stenosis
Aortic valve area (cm^2)	-	> 1.5	1 - 1.5	**< 1**	-
Indexed aortic valve area (cm^2/m^2)	-	> 0.85	0.6 – 0.85	**< 0.6**	-
Peak jet velocity (cm^2)	≤ 2.5	2.6 – 2.9	3 – 4	**> 4**	> 5
Mean gradient (mmHg)	-	< 20	20 – 40	**> 40**	> 60
Dimensionless velocity index	-	> 0.5	0.25 – 0.5	**< 0.25**	-

By convention, severe aortic stenosis is typically defined by an AVA < 1 cm^2 or an indexed AVA (AVAi) < 0.6 cm^2/m^2, as well as a mean gradient > 40 mmHg or a peak velocity > 4 m/s. These values are based on several studies of the natural history of AS.

The concordance of these flow-dependent parameters is contingent upon the preservation of ventricular function. Indeed, in cases of low cardiac output, a significant proportion of patients may exhibit with lower-than-expected transvalvular gradients despite a reduced AVA (<1 cm^2) [7].

The correlation between AVA and transvalvular gradients at varying flow rates is illustrated in **Figure 25**. When cardiac output is diminished, different degrees of aortic stenosis severity may manifest with a similar AVA [127]. This observation highlights the insufficient force of the left ventricle to fully open the AV, which limits the ability of standard hemodynamic measurements to accurately reflect the true severity of the obstruction.

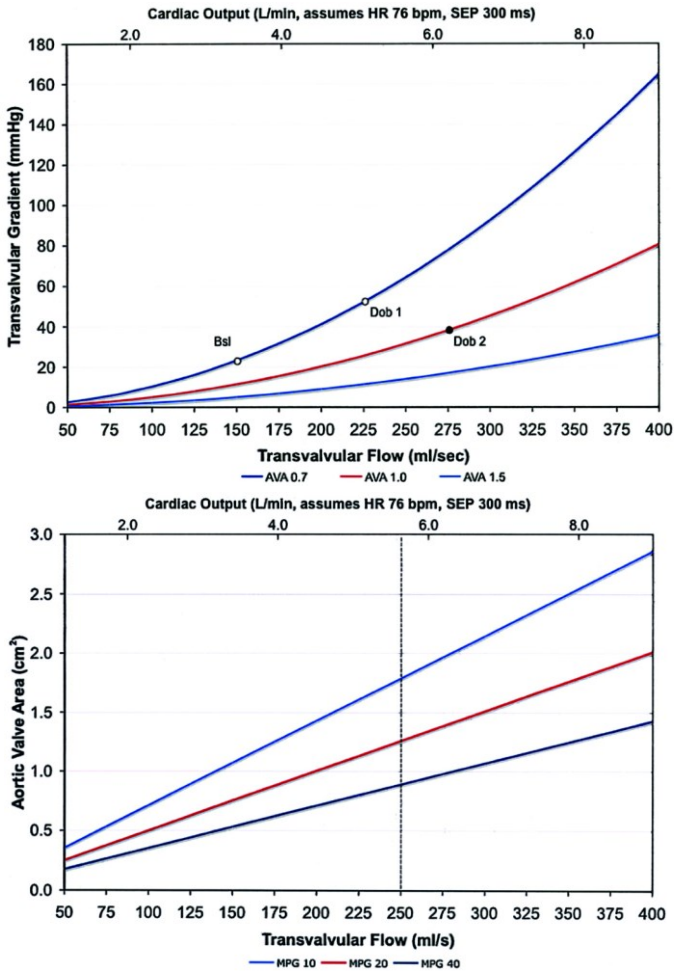


Figure 25: Relationship between mean gradient and flow rate according to the Gorlin equation for different values of AVA (upper panel). Similarly, the linear relationship between AVA and flow rate for various mean gradient values is also displayed (lower panel).

These observations have led to guideline recommendations proposing a stepwise approach in the evaluation of aortic stenosis, including the assessment of LV ejection fraction and indexed stroke volume (**Figure 26**).

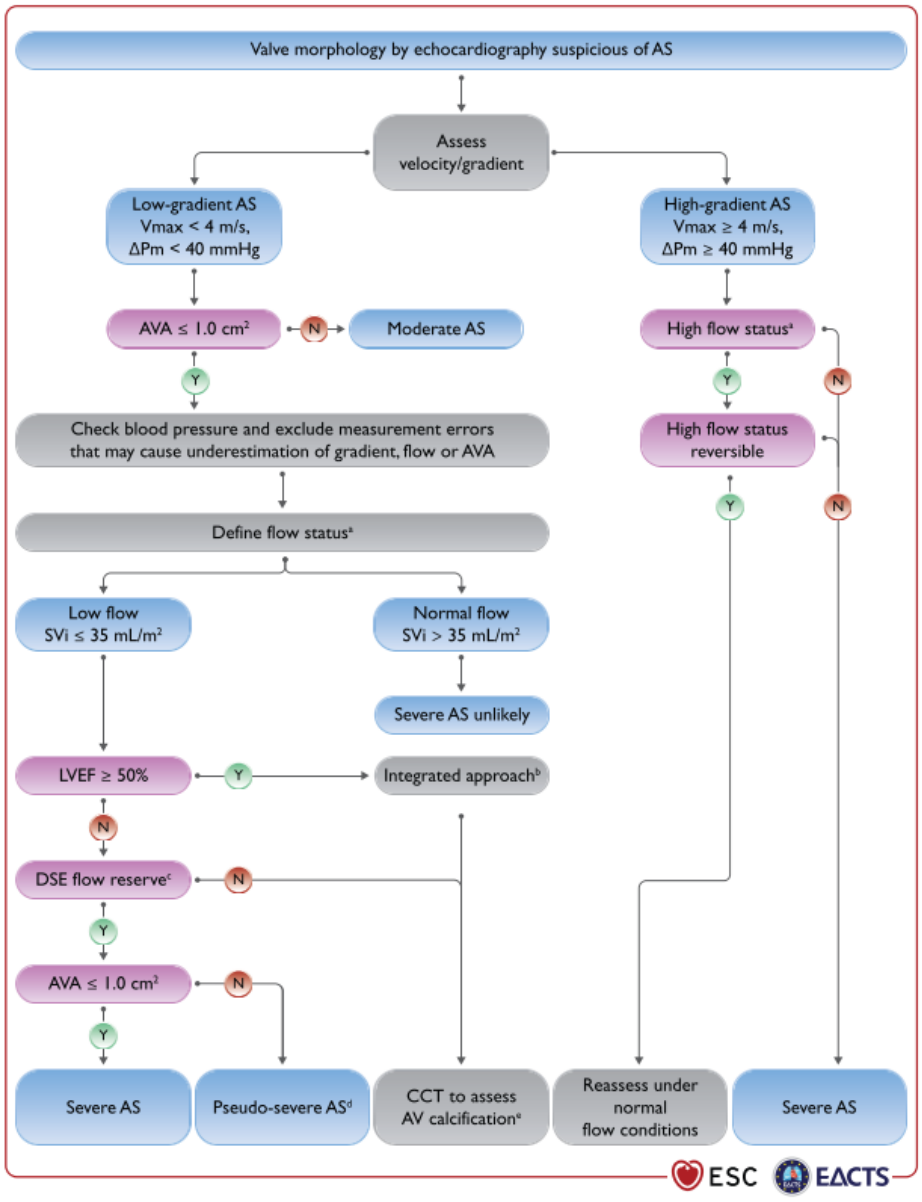


Figure 26: The 2021 ESC/EACTS integrated algorithm for aortic stenosis assessment [5].

Flow and LVEF assessment play a central role in evaluating the severity of aortic stenosis.

Depressed left ventricular function

When a patient presents with a mean gradient <40 mmHg, accompanied by a low-flow state (SVi <35 ml/m²) due to left ventricular dysfunction (LVEF <50%), accurately quantifying the true degree of valve obstruction becomes challenging. This condition is referred to as "classical low-flow low gradient severe AS" and may be observed in approximately 5% to 10% of patients with severe AS [(128)]. The prognosis for these patients is poor, with a 50% survival rate at three years, and a significantly elevated operative risk, ranging from 6% to 33%, depending on comorbidities and the presence or absence of contractile reserve [(128)].

The main diagnostic challenge in these patients is to distinguish true severe AS from pseudo-severe AS and to evaluate contractile reserve, which is defined as an increase in stroke volume of >20% during a Dobutamine stress echocardiography (DSE) [(128,129)]:

True severe AS: an advanced stage of aortic stenosis causing ventricular dysfunction. When compensatory mechanisms are exhausted (due to afterload mismatch, fibrosis, or ischemia), a secondary decrease in gradients is observed despite a significantly reduced AVA. The prognosis depends on the presence of contractile reserve:

- An increase in SV >20% is associated with a favorable outcome from AVR [(129)], with potential LVEF recovery following afterload reduction (Class I, B recommendation) [(97)].
- In contrast, the absence of contractile reserve (<20%) is a strong predictor of surgical mortality and poor long-term prognosis, even following AVR [(128,129)]. However, AVR is not contraindicated and should be considered on an individual basis (Class IIa, C recommendation) [(97)]. TAVI may be a viable option, particularly in patients with high surgical risk.

Pseudo-severe AS: The aortic stenosis is moderate and occurs alongside left ventricular dysfunction of another etiology (e.g., ischemic disease, cardiomyopathy). In this case, heart failure is the primary issue: the left ventricle is unable to generate sufficient force to fully overcome the inertia of the valve and open it completely, which causes the valve area to appear smaller than it actually is. The five-year prognosis for this, in the absence of surgical intervention, is poor, but generally better than in cases of "truly severe" stenosis, particularly when contractile reserve is absent [(130)]. Nevertheless, AVR does not always benefit the patient and is currently not recommended [(130)]. A moderate AS may be well tolerated by a normal ventricle. However, in a dysfunctional ventricle, it can exert a similar impact to that of severe stenosis, which may explain why some studies have still shown benefits from AVR in this population [(130,131)]. Alternative cutoffs have therefore been proposed, such as an effective orifice area <1.2 cm^2 and a mean gradient >30 mmHg under DSE [(129,130)].

In the absence of contractile reserve, it is impossible to accurately determine the true severity of the stenosis, as gradients cannot increase without a corresponding augmentation in flow rate. Consequently, current guidelines recommend either performing a calcium score [(4,5)] or calculating the projected EOA at a normal flow rate (250 ml/min) [(128)].

Patients diagnosed with “classical low-flow, low-gradient severe aortic stenosis” exhibit the poorest prognosis and therefore necessitate specific management recommendations, as detailed above. As a result, these patients are generally excluded from studies investigating the prognosis of aortic stenosis with discordant echocardiographic measurements.

Preserved left ventricular function

The other part of the ESC algorithm (**Figure 26**) addresses AVA-MG discrepancies in patients with preserved left ventricular function. Hachicha et al. investigated these grading discrepancies in patients with preserved LVEF and found a more frequent association with a low transvalvular flow state (SVi <35 ml/m²) [(95)]. However, paradoxical low flow (SVi <35 ml/m² with normal LVEF) cannot explain all cases, as nearly half of the patients with a gradient-area discrepancy have a normal stroke volume (SVi >35 ml/m²) when measured by catheterization [(132)] (**Figure 27**).

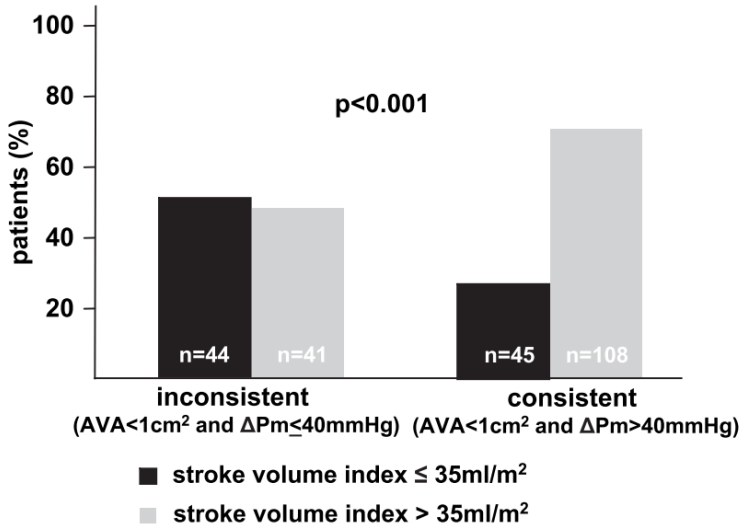


Figure 27: In patients with inconsistent grading (AVA <1 cm² and MG <40 mmHg), low stroke volume is significantly more common than in patients with consistent grading (AVA <1 cm² and MG >40 mmHg). Adapted from Minners et al. Heart, 2010. 96(18): p. 1463-8 [(7)].

Later, Dumesnil et al. proposed a new classification for patients with severe AS based on an AVA < 1cm² and preserved LVEF according to various flow/gradient patterns [(97)] (**Table 5**).

Table 5: Classification of severe aortic stenosis and preserved ejection fraction according to Dumesnil et al. MG stands for mean gradient while SVi denotes stroke volume index. Adapted from Dumesnil et al. Eur Heart J. 2010;31:281-9 [97].

	Concordant AVA/MG	Discordant AVA/MG
Concordant Flow/LVEF	**Group 1** **Normal flow, high gradient** • SVi ≥ 35ml/m² • MG > 40 mmHg	**Group 2** **Normal flow, low gradient** • SVi ≥ 35ml/m² • MG < 40 mmHg
Discordant Flow/LVEF	**Group 3** **Low flow, high gradient** • SVi < 35ml/m² • MG > 40 mmHg	**Group 4** **Low flow, low gradient** • SVi <35ml/m² • MG > 40 mmHg

Currently, the true severity of these different patterns, along with their prognostic and therapeutic implications, remains largely uncertain. The clinical role of this paradoxical low-flow state despite preserved LVEF, continues to be the subject of intense debate in the literature. This issue was the focus of my first research topic and will be discussed in detail in Part 3.

2.2.11. Treatment

The treatment of aortic stenosis is a major public health concern due to the high prevalence of the disease. Despite a pathophysiology that leads to slow progression coupled with the emergence of numerous potential therapeutic targets, to date no pharmacological intervention has proven effective in slowing its progression. Therefore, aortic valve replacement remains the only intervention capable of improving patient outcomes. In other words, a mechanical solution is provided for a mechanical problem, despite a growing understanding of the cellular and molecular pathways involved, making

aortic stenosis one of the last cardiovascular diseases for which we still lack effective pharmacological options [133].

2.2.11.1. Medical therapy

Over the past 20 years, numerous therapeutic targets identified through our understanding of underlying pathophysiological processes have been investigated. Although these molecules effectively modulate these processes, all randomized controlled trials (RCTs) attempting to slow the progression of aortic stenosis have been unsuccessful. **Figure 28** offers an overview of the principal therapeutic targets and associated pharmacological agents studied.

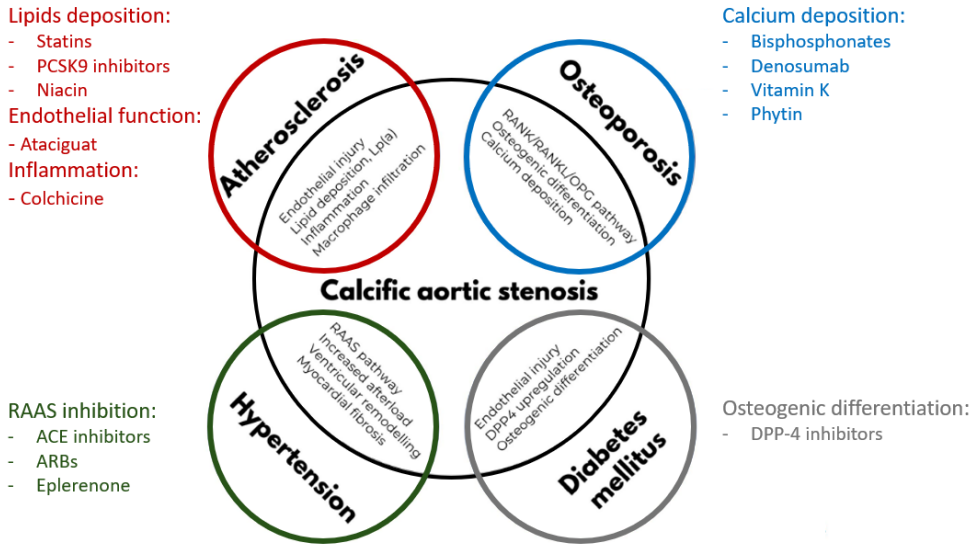


Figure 28: Diagram depicting the proposed shared mechanisms between calcific aortic stenosis and other related pathologies, that have been or are currently the focus of clinical studies. DPP-4 stands for dipeptidyl peptidase-4; Lp(a) refers to lipoprotein (a); OPG is osteoprotegerin; RAAS denotes renin–angiotensin–aldosterone system; RANKL is the receptor activator of the nuclear factor-κB ligand. Adapted from Otto CM, Heart 2020;106:1783 [134].

Currently, the only therapeutic class recommended by international guidelines is renin-angiotensin system blockers. These are the only agents offering potential benefits for myocardial remodeling [135] prior to symptom onset and following TAVI or SAVR [4,5]. Additionally, coexisting hypertension should be managed to prevent added afterload.

Aortic stenosis is most often diagnosed at advanced stages, limiting the potential for early intervention in both routine practice and clinical studies. One primary reason for the failure of these studies is likely the timing of interventions, which may occur too late [136]. Valvular atherosclerosis plays a major role in the onset of the disease, but gradually diminishes as calcification processes take over in a self-perpetuating cycle. Consequently, interventions targeting inflammation and lipid deposition are likely to exhibit very limited effectiveness [137]. The variety of cellular pathways involved in calcification also partially accounts for the therapeutic failures, as no studies have concurrently investigated the blockade of multiple signaling pathways. Finally, the follow-up duration of these studies is generally short (2 to 4 years) [138], meaning that a lack of short-term effects does not necessarily imply an absence of long-term benefits. In this regard, there is a need for diagnostic tools to facilitate therapeutic monitoring. Molecular imaging with PET-CT could provide valuable support to clinicians. Several studies have established endpoints based on 18F-NaF uptake, which is directly correlated with valvular calcification activity [125,126]. Additionally, other markers are also being developed to target additional molecular pathways.

Lipoprotein(a) (Lp(a)) is the main lipoprotein transporting oxidized phospholipids (OxPL) on apolipoprotein B-100 and it is a well-established genetic risk factor for calcific AS and coronary artery disease [30]. The pro-osteoblastic effects of Lp(a) are mediated by a phenotypic change in VICs via the actions of the Ox-PL [52]. Reducing Lp(a) levels to slow the progression of AS is a promising target [139-141], but its efficacy has yet to be confirmed in prospective randomized trials. Niacin, a potential therapeutic agent that can

lower Lp(a) in a dose-dependent manner, is currently being investigated in the Early Aortic Valve Lipoprotein(a) Lowering Trial (EAVaLL, NCT02109614). Another promising study lead by Novartis is evaluating Pelacarsen, a hepatocyte-directed antisense oligonucleotide that targets LPA mRNA, reducing Apo(a) production and lowering Lp(a) levels. This randomized, double-blind, placebo-controlled, multicenter trial (NCT05646381) is investigating whether Lp(a) lowering (inclusion criterion: Lp(a) ≥175 nmol/L) can reduce the mid-term risk of progression in patients with mild to moderate aortic stenosis. The results are highly anticipated, as an effective medical therapy capable of modifying the underlying pathophysiology and slowing aortic stenosis progression remains an important unmet clinical need.

2.2.11.2. Valve replacement

The prognosis for aortic stenosis was poor until the introduction of the first surgical valve replacements in the 1960s. Since then, advancements in surgical techniques have established valve replacement as the gold standard for managing severe aortic stenosis, making it the only intervention shown to improve both symptoms and survival [142,143].

Surgical valve replacement (SAVR) is performed via sternotomy or mini-sternotomy and involves the removal of the diseased valve which is then replaced with a substitute: homograft, biological, or mechanical prosthesis. Each type of substitute presents numerous advantages and disadvantages, and the selection is made thoughtfully after a discussion with the patient [144,145]. However, observational studies have indicated that surgery in some subgroups—such as older patients, those with multiple comorbidities, or those with left ventricular dysfunction—carries a high risk of perioperative complications [146-148]. These high-risk patients were initially the target group for transcatheter aortic valve replacement (TAVR), which involves deploying a bioprosthesis mounted on a catheter directly onto the diseased valve [146].

Subsequently, TAVR has been gradually offered to patients with lower surgical risk [149-152] and is now recommended as a first-line option for patients over 65 years according to AHA guidelines [4] and over 75 years of age according to ESC guidelines [5]. Currently, there is no clear evidence demonstrating a medium-term clinical outcome advantage for one technique over the other [153].

The primary requirement for referring a patient for valve replacement, whether surgical or percutaneous, is to confirm the severity of the valve obstruction, as discussed above. Once the severity is established, a step-by-step approach is encouraged and recommended by both European and American guidelines [4,5] (**Figure 29**).

The first driver for AVR is the presence of symptoms. Identifying these symptoms can be challenging, as they may present atypically, stem from mixed origins due to associated comorbidities, or be underreported due to the inherent underestimation common in chronic conditions. Therefore, performing an exercise test to unmask symptoms or detect a drop in systolic blood pressure during exertion is recommended. The other major driver for AVR is the presence of left ventricular dysfunction (LVEF <50%) regardless of symptom presence. Patients with severe aortic stenosis who exhibit symptoms or an LVEF <50% (Class I indications) are at high risk of major cardiovascular events and benefit significantly from valve replacement [8,9,143,154-156]. However, the ideal timing for intervention remains hotly debated and will be discussed later in Part 4. Moreover, several additional risk-associated factors have been proposed as indications for AVR in asymptomatic patients, including: an LVEF <55%, a peak jet velocity >5 m/s, severe calcification assessed by CCT, velocity progression >0.3 m/s per year, and markedly elevated BNP levels.

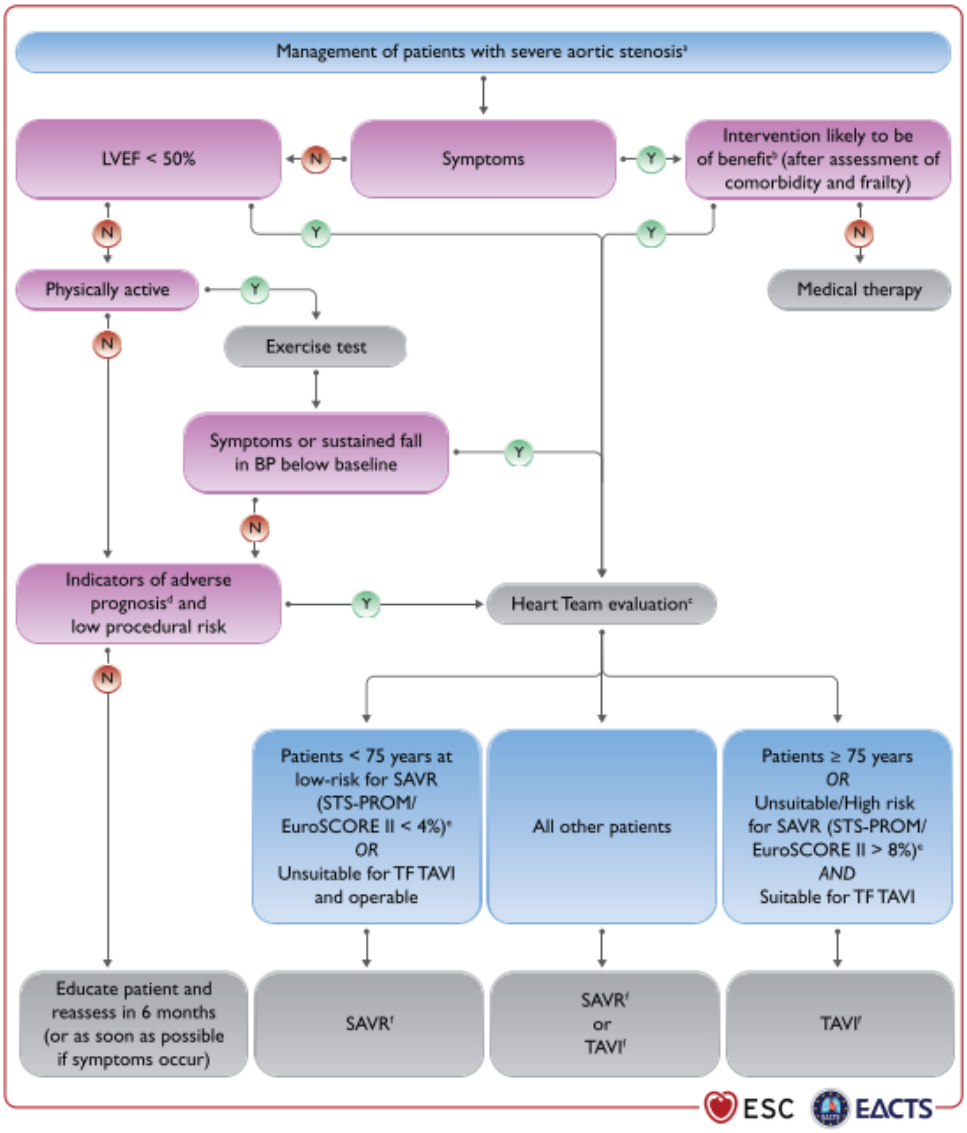


Figure 29: ESC/EACTS Guidelines on the management of severe aortic stenosis. From Vahanian et al. Eur Heart J. 2021.

Part 3. DISCORDANT GRADING: THE DEBATE

This section aims to provide an overview of the causes of the resultant discrepancies in the prognosis of discordant low-gradient aortic stenosis. In order to do so, we will review the exact definitions and their inherent issues, as well as the methodological and physiological causes of said discrepancies. Finally, we will examine the studies that shed light on the topic from alternative perspectives, such as calcium load, disease progression over time, and markers of myocardial damage.

3.1. Definitions

Defining severe aortic stenosis is a critical first step in patient management, as recommended by current guidelines [4,5] (**Figure 29**). Although seemingly straightforward, Part 2 has already provided an overview of the most frequently encountered challenges associated with this process. Specifically, severe aortic stenosis is defined as an AVA of <1 cm^2 (indexed AVA <0.6 cm^2/m^2) with a mean transvalvular gradient ≥40 mmHg. When the echocardiographic criteria are concordant, diagnosis is relatively simple. However, up to 30% of patients present discordant findings, such as: lower-than-expected peak transvalvular velocities and mean pressure gradients (MG ≤40 mmHg) despite SAS based on AVAi (<0.6 cm^2/m^2) [7]. In cases of left ventricular dysfunction, transvalvular gradients decrease due to reduced antegrade flow. This first cause of AVA-gradient discordance is known as "classical low-flow, low-gradient severe AS" and is characterized by an AVA of <1 cm^2 (indexed AVA <0.6 cm^2/m^2), a mean gradient of <40 mmHg, and an LVEF of <50%. This patient subgroup has been previously discussed, and their poor prognoses are well documented and undisputed in the literature. In 2007, Hachicha[95] introduced another form of low-gradient severe aortic stenosis, one characterized by a paradoxical reduction in the transvalvular flow despite normal LVEF. This new cause of AVA-gradient discordance is referred to as "paradoxical low-flow, low-gradient severe AS" and is defined by an AVA of <1 cm^2 (indexed AVA <0.6 cm^2/m^2), a mean gradient of <40 mmHg, a stroke volume index of <35 ml/m^2, and an LVEF of ≥50%. Finally, a

reduced gradient of <40 mmHg can be observed with an AVA <1 cm², despite normal LVEF and transvalvular flow; a condition referred to as "normal-flow, low-gradient severe AS." All of these distinct entities are depicted in **Figure 30**.

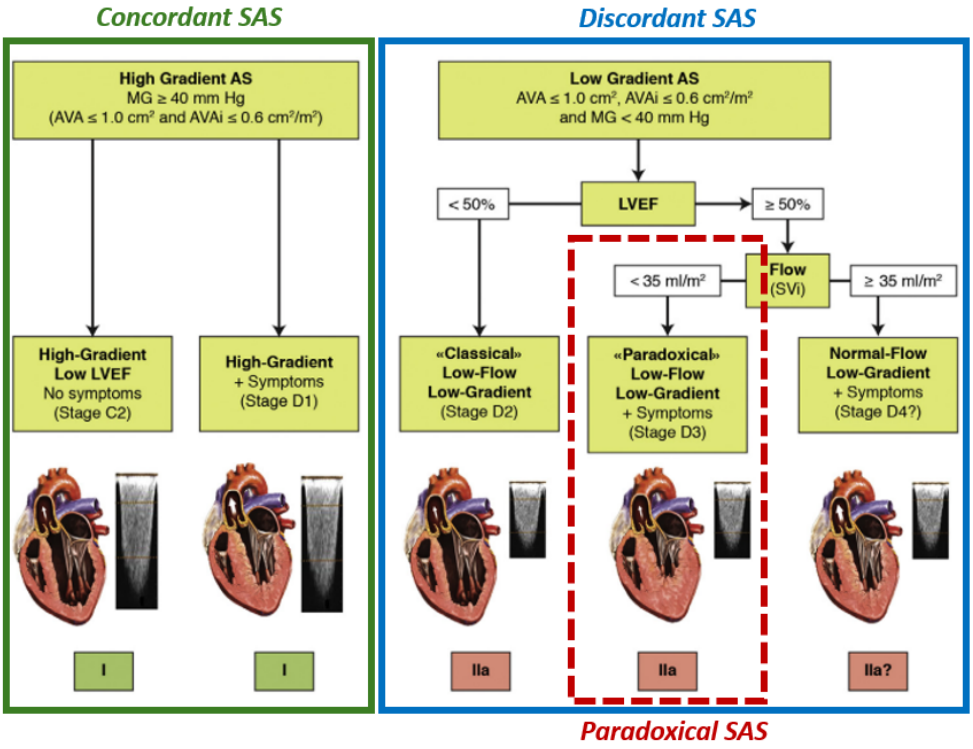


Figure 30: The classification of AS types based on their respective concordance or discordance in standard echocardiographic parameters as well as flow/LVEF pattern entities. Adapted from Clavel et al. JACC: Cardiovascular Imaging 2017;10:185-202 [(157)].

Currently, the existence of this discordant low gradient severe AS (DLG-SAS) leads to uncertainty regarding the actual severity of the stenosis, prognostic implications, and therapeutic management. Indeed, certain authors consider this entity to be a more advanced form of AS [(158)], with poor prognoses under conservative treatment [(99)], while others have provided

evidence that it is a more benign form of AS with an outcome similar to that of moderate AS (MAS) [159,160].

The initial and most critical step in addressing the conflicting data regarding the true severity of DLG-SAS is to clarify the often ambiguous nomenclature found in the literature. There is considerable variability and inconsistency in the terminology used to describe these patients. Some authors refer to this condition as "paradoxical low-flow AS," "paradoxical low-gradient AS," or "discordant low-gradient AS," which creates confusion between AVA/gradient discordance and flow/LVEF discordance. The term "paradoxical" should be strictly applied to specific flow/LVEF patterns. Consequently, these terms are not interchangeable and frequently result in misunderstandings.

Another source of discrepancies in DLG-SAS prognosis lies in the significant variability in patient inclusion and classification criteria across studies. This inconsistency is likely due to the diverse nomenclature used, as shown in **Table 6**. Indeed, studies reveal variations in the applied LVEF and SVi cutoffs, inconsistent placement of equality signs, and differing practices regarding AVA indexing. Caution is therefore needed when comparing study results, as their designs vary significantly despite addressing the same issue.

Table 6: Definitions of patient inclusion criteria in the main studies investigating the prognosis of discordant aortic stenosis. Studies involving patients with an LVEF <50% or lacking survival data were excluded.

Author	Year	N	AVA	AVAi	MG	Flow	LVEF
Hachicha et al.	2007	512	.	≤0.6	.	< or ≥ 35	>50
Barasch et al.	2008	215	.	≤0.6	< or ≥ 30	.	≥50
Belkin et al.	2011	248	<1	.	<30 or 30-40 or >40	.	≥50
Jander et al.	2011	1525	<1	.	< or ≥ 40	< or ≥ 35	≥55
Tarantini et al.	2011	102	≤1	.	≤30	.	>50
Clavel et al.	2012	1589	≤1	≤0.6	< or ≥ 40	≤ or > 35	≥50
Lancellotti et al.	2012	150	<1		< or ≥ 40	< or ≥ 35	≥55
Clavel et al.	2013	646	.	> or ≤ 0.6	< or ≥ 40	< or ≥ 35	≥50
Eleid et al.	2013	1704	<1	.	< or ≥ 40	< or ≥ 35	≥50
Mohty et al.	2013	768	≤1	.	< or ≥ 40	< or ≥ 35	>50
Mehrotra et al.	2013	113	<1	.	≤40	< or ≥ 35	≥55
Maes et al.	2014	349	<1	<0.6	≤ or > 40	< or ≥ 35	≥50
Maor et al.	2014	409	≤1	.	<40	<37 or 37-42 or >42	≥50
Eleid et al.	2015	405	<1	.	<40	<38 or 38-43 or 43-48 or >48	≥50
Kamperidis et al.	2015	191	.	<0.6	≤ or > 40	< or ≥ 35	≥50
Rezzoug et al.	2015	542	.	<0.6 or 0.6-0.9 or >0.9	< or ≥ 40	≤ or > 35	>50
Tribouilloy et al.	2015	809	< or ≥ 1	< or ≥ 0.6	< or ≥ 40	< or ≥ 35	≥50
Yamashita et al.	2015	385	.	<0.6 or 0.6-0.85	< or ≥ 40	< or ≥ 35	>50
Rusinaru et al.	2018	1450	<1	<0.6	.	<30 or 30-35 or >35	≥50
Boulif et al.	2021	266	.	< or > 0.6	< or ≥ 40	< or ≥ 35	>50
Slimani et al.	2021	147	.	< or > 0.6	< or ≥ 40	< or ≥ 35	>50
Galian-Gay et al.	2022	1391	<1	.	< or ≥ 40	≤ or > 35	≥50
Yamashita et al.	2024	781	.	.	< or ≥ 40	< or ≥ 35	≥50

3.2. Prognostic considerations

This section provides a brief overview of the main studies addressing the prognosis of DLG-SAS with preserved LVEF, often with stratification based on flow status. In order to do so, we will distinguish between studies focused on the natural history of the disease and those investigating post-operative survival.

3.2.1. Natural history

DLG-SAS, an advanced form

As previously described, in 2007 Hachicha et al. [95] paved the way by stratifying DLG-SAS based on flow status for the first time. In this retrospective study involving 512 patients with preserved LVEF, a poorer prognosis was demonstrated when SVi was <35 ml/m², despite a similar prevalence of comorbidities. However, after adjusting for age, sex, valvulo-arterial impedance (Zva), and treatment type, the results were no longer significantly different. The authors concluded that reduced flow—despite preserved LV function—reflects a more advanced stage of the disease.

Subsequent studies reached similar conclusions. In 2012, Clavel et al. [158] published a retrospective study comparing three groups of patients: moderate AS (MAS), paradoxical low-flow, low-gradient severe AS (PLFLG-SAS), and high-gradient severe AS (HG-SAS). Overall and cardiovascular survival rates were lower in the PLFLG-SAS group compared to the other groups. However, unadjusted results should be interpreted with caution, as survival was calculated independently of whether a valve replacement was performed during follow-up. The authors further adjusted the analyses for age and AVR as a time-dependent variable and showed a poorer prognosis for DLG-SAS patients, despite a lower referral rate for surgery in this group. Surprisingly, the prognosis for HG-SAS and MAS appeared better and similar between the two groups. Notably, the PLFLG-SAS group was older and had a higher proportion of women, along with a greater prevalence of coronary artery disease and hypertension. Additionally, this group exhibited higher

valvulo-arterial impedance, faster heart rates, and lower measures of body surface area, LVEF, LV end-diastolic volume, and transvalvular flow rate. However, none of these variables, apart from age, emerged as independent prognostic factors in the multivariate analysis. Consequently, the impact of these comorbidities on survival could not be fully assessed.

Also in 2007, Lancellotti et al. [161] published a study using the flow/gradient classification introduced by Dumesnil et al. [97] and reported a three-year higher rate of cardiovascular events in the LF/LG group. They stated that, compared with the other AS categories, patients with NF/LG have better cardiac event-free survival. Conversely, both LF/LG and LF/HG entities are associated with poorer outcomes. Finally, patients with NF/HG present an intermediate prognosis when compared with the other groups. Nevertheless, it is important to note that these analyses were based on a very small sample size (N < 15 patients in two groups), and the multivariate statistical adjustment did not include any demographic variables. Instead, it included peak velocity, which is collinear with gradients and flow.

A year later, Eleid et al. [99] stratified their cohort of 1704 patients using the same classification system. They confirmed that patterns based on flow/gradient were associated with all-cause mortality after adjusting for confounding variables through inverse probability weighting (included variables: age, sex, obesity, hypertension, heart failure, AVA, and LVEF). Consistent with previous studies, the LF/LG group was associated with a poorer prognosis compared to the other groups. However, this group was small (N = 53, representing 3% of the cohort), with half of the patients being afflicted by atrial fibrillation, and LVEF was significantly lower than that in the other groups.

Finally, Mohty et al. [162] published a noteworthy study in 2013, in which the flow/gradient classification was performed invasively using cardiac catheterization. Their cohort comprised 768 patients with SAS and preserved cardiac function, most of whom underwent valve replacement during follow-up. Several statistical adjustment models were applied to

assess the impact on survival, including the use of AVR as a time-dependent variable. Additionally, a propensity score model was also developed to compare the risk of valve replacement versus conservative treatment. This study, which had a follow-up duration of up to 10 years, revealed a poor prognosis for the PLFLG group, regardless of whether they were treated medically or surgically, even after multiple adjustments. However, no difference in prognosis was observed between the NFHG and NFLG groups following adjustment, which appears counterintuitive.

DLG-SAS, an intermediate form

In 2011, Jander et al. [163] published findings that contradicted those of Hachicha et al. [95]. They compared the prognosis of low-gradient severe AS (DLG-SAS) to that of moderate AS and high-gradient severe AS in a cohort of 1525 patients, ultimately demonstrating that DLG-SAS yielded a prognosis (cardiovascular death, AVR, or hospitalization for heart failure) similar to moderate AS and significantly better than high-gradient SAS. Surprisingly, they did not identify any associations between flow status and survival; however, it is important to note that patients had to have an LVEF of >55% to be included. These results remained consistent following a limited multivariate adjustment. Resultantly, the authors concluded that DLG-SAS does not represent a more advanced form of the disease.

The presence of comorbidities and their associated complications more frequently occurs in patients with LFLG-SAS, and may partly contribute to the reduced stroke volume and increased risk of mortality and morbidity observed in previous studies [164]. Indeed, subsequent studies that applied stricter exclusion criteria for comorbidities reported different outcomes.

In 2014, Maes et al. [160] retrospectively studied the outcomes of 349 patients with severe AS based on AVAi (<0.6 cm^2/m^2). Patients with active malignancies, in the advanced stages of cognitive disorders, or with severe renal failure were excluded. They demonstrated that DLG-SAS yielded better prognoses than HG-SAS, regardless of flow status. In this study, SVi was

found to have no impact on survival; interestingly, they found that approximately 82% of DLG-SAS patients experienced an increase in their mean transvalvular gradients over time, with half progressing to HG-SAS by the end of follow-up. Similar observations were made by Rezzoug et al. [165] in a prospective study including elderly patients (>80 years) with AS. The five-year overall survival rate was found to be significantly worse in HG-SAS than in any of the other groups (moderate AS or DLG-SAS). The survival rate was comparable among DLG-SAS patients, regardless of whether they had normal or low flow. However, it should be noted that the sample size was extremely small for certain groups (N = 9 for HG-SAS and 23 for DLG-SAS further stratified by flow status).

In 2015, Tribouilloy et al. [159] published a retrospective study examining the natural history of 809 patients diagnosed with moderate AS, high-gradient SAS, or low-gradient SAS, stratified by flow status. Notably, the researchers observed that while unadjusted analyses indicated a lower 4-year survival rate in the PLFLG group, adjusted analyses that accounted for comorbidities revealed survival rates that were intermediate between those of the moderate and HG groups. This highlights the significant impact of comorbidities as confounding factors in survival analyses. Additionally, the authors reported that, under both medical and surgical management, symptomatic LF/LG SAS did not present an excess mortality risk when compared to asymptomatic moderate AS.

More recently, other studies have argued that DLG-SAS represents an intermediate stage of the disease that subsequently progresses to HG-SAS. Yamashita et al. [166] also reported similar findings in a Japanese cohort of 385 patients following multiple adjustments. More recently, in 2022, Galian-Gay et al. [167] published data on a Spanish cohort of 1391 patients, demonstrating that the LFLG AS group exhibited a lower need for AVR compared to the HG group, with similar needs to the NFLG group, without any differences in mortality. Furthermore, AVR had a lower impact on LFLG

AS compared with HG AS. The findings of the study demonstrated that LFLG AS has an intermediate clinical risk profile between the HG and NFLG groups.

3.2.2. Post-operative survival

Post-operative survival has also been investigated by numerous research groups; however, their findings are as inconsistent as those from studies on the natural history of the disease. While the majority of studies agree that valve replacement is beneficial for patients with DLG-SAS [158,160,167-172], the extent of this benefit compared to other forms of the disease, however, varies between studies. Ultimately, there has been study that did not find any advantages that valve replacement has over medical treatment in these patients [159].

In their meta-analysis, Dayen et al. (2015) confirmed the benefits of AVR across all severity groups, having calculated a pooled mortality reduction of 56% in PLFLG patients undergoing AVR, similar to the 52% observed in NFLG patients. Patients with HG-SAS were found to derive the greatest benefit from AVR, with a 75% reduction in mortality risk. The researchers' results also highlighted the lower referral rate for AVR among LFLG patients compared to those with HG-SAS.

Interestingly, studies analyzing post-operative survival consistently yielded better outcomes in patients with HG-SAS that in those with DLG-SAS, with this difference being even more pronounced in low-flow states. The primary explanation advanced by Dayen et al. is that many pre-existing comorbidities persist even after AVR. The high prevalence of low flow in the AS population is unsurprising, as this group is predominantly elderly and frequently burdened by comorbidities such as systemic hypertension, coronary artery disease, diabetes, atrial fibrillation, mitral regurgitation, tricuspid regurgitation, and mitral stenosis. These conditions are often accompanied by more pronounced symptoms and complications, such as adverse LV

remodeling and systolic dysfunction. All these parameters are known to influence post-operative mortality.

3.3. Methodological causes of discrepancies

This section provides a review of the sources of measurement errors in assessing echocardiographic severity parameters for classifying aortic stenosis severity. We will examine the acquisition and calculation of these parameters and critically evaluate the threshold values chosen in the guidelines.

3.3.1. Measurements errors

Accurately measuring transvalvular gradients, AVA, and stroke volume using Doppler is of utmost importance. Such precision is crucial because, when diagnosing low-gradient severe AS, there is a significant risk of misclassification. The clinician might mistakenly overestimate the severity of moderate AS, classifying it as severe, or conversely, underestimate the severity of true severe AS, thereby leading to an incorrect diagnosis and potentially inappropriate management.

Proper recording of peak velocity necessitates correct patient positioning, meticulous adjustment of the probe's placement and angulation, and thorough exploration of multiple acoustic windows. As detailed in the theoretical background section, even a slight misalignment of up to 15° between the probe and the jet direction can lead to a minor underestimation. However, small errors in measuring peak velocity may result in significant underestimation of transvalvular gradients due to the squared function in the simplified Bernoulli equation. Furthermore, reliance on the apical window alone is inadequate. Thaden et al.'s study of a cohort of 100 patients demonstrated that the maximum velocity is obtained from the right parasternal window in up to 50% of cases [(173)].

The continuity equation, utilized to calculate both stroke volume and AVA, relies heavily on an accurate LVOT diameter measurement. In fact, most classification errors originate from inaccuracies in this measurement, along with the theoretical assumptions underlying it. First, the precise theoretical positioning of the measurement is debated and can vary in practice depending on factors such as annular calcifications or septal hypertrophy, which may lead to an inaccurately small LVOT diameter measurement. Furthermore, the continuity equation assumes that the LVOT area is circular; however, numerous studies have demonstrated that it is actually ellipsoidal [85,86,88]. The standard anteroposterior measurement taken in the parasternal long-axis view typically measures the minor axis of the ellipse rather than the major sagittal axis. This results in an underestimation of the LVOT area, leading to an underestimation of the stroke volume passing through it by approximately 10–15% [88,174]. In the continuity equation, any error in the LVOT area calculation is squared, thereby amplifying its impact and introducing significant inaccuracies. Misclassification of AS can occur when a smaller LVOT diameter is measured, leading to underestimation of both stroke volume and AVA. Calculating the dimensionless velocity index (DVI) is an effective means to avoid errors associated with LVOT measurement. Additionally, if the DVI value is <0.25 in a suspected case of severe stenosis, it can provide bolster the clinician's confidence regarding the accuracy of the LVOT measurement and the diagnosis.

Another way to measure AVA is through a visual assessment of its maximum opening area using planimetry. As explained in the theoretical introduction, this area corresponds to the geometric orifice area (GOA), which is by definition larger than the effective orifice area (EOA). This difference arises because it neglects the coefficient of orifice contraction, which accounts for the convergence of flow lines downstream of the orifice, and is strongly influenced by the valve's opening shape (**Figure 31**). Indeed, the sharper the angle between the aorta and the valve leaflets, the further the vena contracta forms, increasing the coefficient of contraction through greater flow acceleration. Planimetry cannot be used to estimate EOA; therefore, a

GOA >1 cm² does not rule out the presence of severe stenosis. However, a GOA <1 cm² suggests that the stenosis is likely severe, although this cutoff has not been validated for this measurement. Specific thresholds would likely need to be established for routine clinical use [157].

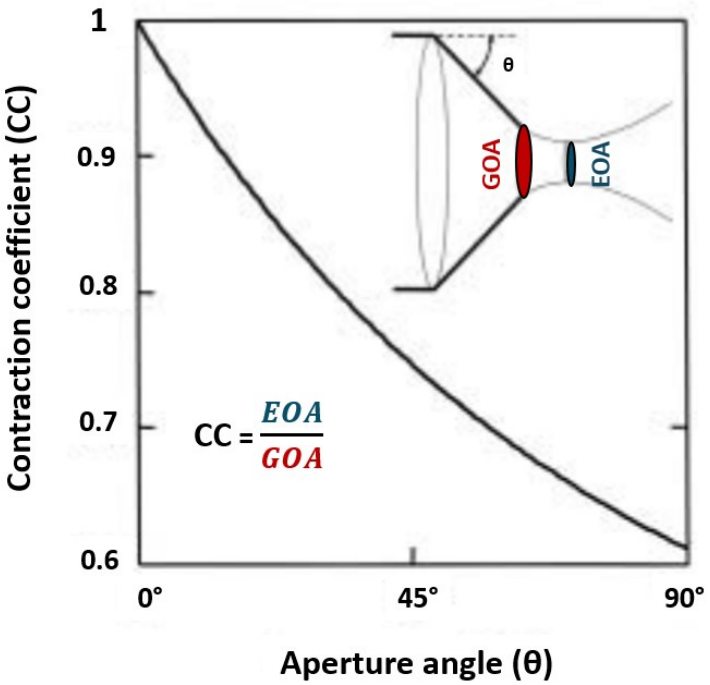


Figure 31: Variation of the contraction coefficient (CC) as a function of the aperture angle (θ) for a rigid sharp-edged aortic stenosis. Adapted from Damien et al. J Heart Valve Disease 2006;15, No.5 [84].

3.3.2. Cutoffs

Guidelines for grading aortic stenosis were initially established based on data derived from invasive measurements that reflect the anatomic valve area [7]. The Gorlin AVA is an adjusted EOA designed to approximate the geometric area [104]. Currently, Doppler echocardiography is considered the gold standard for assessing AS and serves as the basis for clinical decision-

making. However, the Doppler-derived EOA is typically lower than the Gorlin-derived AVA because it accounts for the coefficient of contraction and is based on maximum pressure gradients at the vena contracta, rather than the net pressure gradient measured upstream following the pressure recovery phenomenon. Consequently, it is logical that the correlation between AVA and mean gradient differs between these two modalities (**Figure 32**).

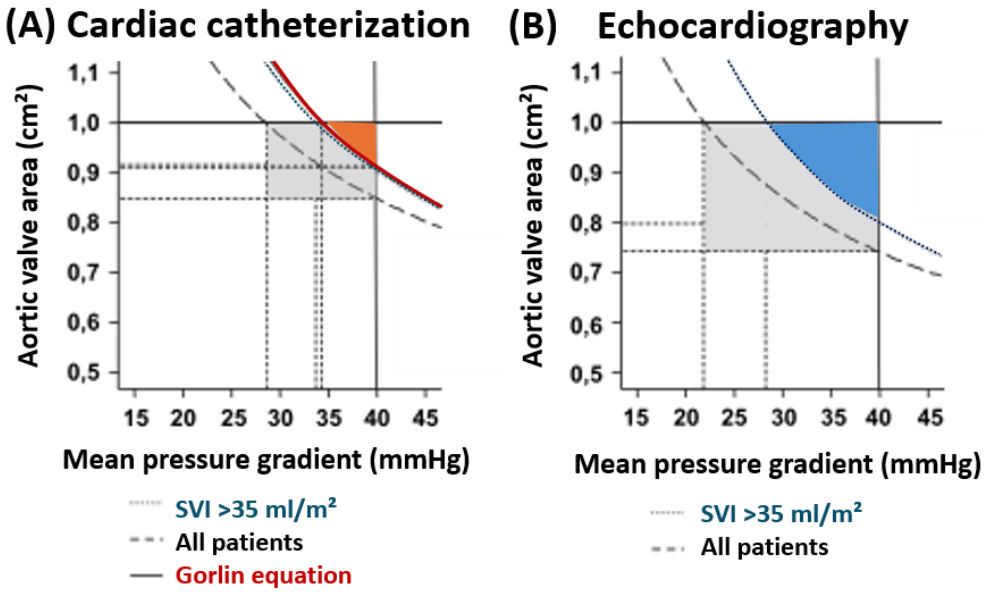


Figure 32: Extent of inconsistent grading of the severity of AS in patients with low- and normal-stroke volume and LVEF >50%. (A) The fitted curves for data pairs of mean pressure gradient (MPG) versus AVA from cardiac catheterization for the entire study population are limited to patients with SVI >35 ml/m² and the hypothetical Gorlin-based curve with a CO of 6 l/min, a SEP of 0.33 s, and a HR of 70/min. All three fitted curves intersect to the left and below the respective cut-off values of AVA 1 cm² and MPG 40 mmHg given in current guidelines. (B) Data from echocardiography for all patients, and limited to patients with an SVI >35 ml/m², show a similar but more pronounced pattern, indicating that inconsistent grading is more prevalent with non-invasive assessment of the SAS than with cardiac catheterization. Adapted from Minners et al. Heart 2010;96(18):1463-8 [(132)].

The analysis of **Figure 32** presents several significant findings. First, regardless of the measurement modality, as the disease progresses, the valve area consistently decreases, ultimately falling below the critical <1 cm^2 threshold. In contrast, transvalvular mean gradients lag behind, remaining below 40 mmHg. This disparity indicates a temporal discrepancy resulting from the severity thresholds defined in the guidelines, which leads to an AVA/MG discordance. Secondly, the colored area between the intersection point (AVA = 1 and MG = 40) and the fitted curve (for SVI >35 ml/m^2) in the diagrams varies based on the measurement modality. Specifically, the area defined by the curve generated using the Gorlin equation (orange) is smaller than that measured by Doppler (blue). This observation implies that inconsistent grading is more prevalent with non-invasive assessments of SAS than with cardiac catheterization. Finally, the AVA/MG discordance becomes even more pronounced when comparing the fitted curves for the total population (low and normal flow), with Doppler measurements exhibiting a greater degree of inconsistency.

New corresponding AVA/MG severity thresholds can be established by examining the intercepts of the curves presented earlier (**Figure 32**). Using the Gorlin formula, a gradient of 26 mmHg is sufficient to correspond to an AVA of 1 cm^2. Conversely, a mean gradient threshold of 41 mmHg actually corresponds to a smaller-than-expected AVA (0.8 cm^2). A summary of these updated AVA/MG pairings is provided in **Table 7**.

Table 7: Relationship between AVA and MG according to the Gorlin equation as measured by cardiac catheterization. From Carabello et al. N Engl J Med, 2002 [(175)].

Aortic valve area (cm^2)	Mean gradient (mmHg)
4	1.7
3	2.9
2	6.6
1	26

0.9	32
0.8	41
0.7	53
0.6	73
0.5	105

Similar results were reported by Kebed et al., who investigated the inconsistency of guideline cutoffs in a cohort of 916 patients [176]. Their study demonstrated that the AVA calculated using the Gorlin equation more accurately represented the AVA derived from real-life datasets, further confirming the hemodynamic inconsistency of the guideline-recommended cutoffs. Moreover, they also confirmed that the incidence of AVA/MG discrepancies was higher when LVEF was reduced.

To address this challenge, some researchers have suggested lowering the AVA threshold for defining severe AS to 0.8 cm^2 to align with a mean gradient of 40 mmHg [132,157]. However, modifying the severity criteria could risk delaying the treatment of symptomatic or high-risk patients. As such, the preferred approach for now appears to be retaining the current thresholds: AVA <1 cm^2 for sensitivity and a mean gradient of ≥40 mmHg for specificity [157].

3.3.3. Indexation of measurements

Another limitation of using uniform cutoffs is that, while they may suit most patients [7], they may not be appropriate for those at the extremes. Patients with smaller body sizes naturally have proportionally smaller cardiac chambers, which results in a reduced LVOT area, smaller AVA, and physiologically lower stroke volume. Consequently, a small AVA in a patient with a small body size may actually represent moderate AS and be associated with a low gradient. In such cases, calculating the indexed AVA is recommended, with a value >0.6 cm^2/m^2 ruling out severe AS.

On the contrary, indexing AVA to body surface area may overestimate the severity of AS in obese patients. To address this limitation, two approaches have been proposed: firstly, using a lower AVAi cutoff (<0.5 cm^2/m^2) to define severe AS in individuals with a body mass index ≥30 kg/m^2 [157] and lastly, adopting alternative indexation methods, such as indexing AVA to height (<0.45 cm^2/m), as suggested by Tribouilloy et al. [177].

3.4. Physiological causes of discrepancies

3.4.1. Flow status

The flow-dependent nature of the echocardiographic parameters has previously been extensively described. As such, stroke volume emerges as a key factor in the low-gradient state. However, a paradoxically low flow (SVi <35 ml/m^2 with normal LVEF) cannot explain all cases, as nearly half of those patients with a discordance between gradient and AVA had a normal stroke volume when measured by catheterization [132].

Low-flow status was arbitrarily defined by Hachicha et al [95] as having an SVi of <35ml/m^2. In their 2007 paper, the authors did not provide an explanation for the rationale underlying the selection of this threshold for defining low cardiac output. However, considering that a normal cardiac index ranges from 2.5 to 4 $L/min/m^2$ and that the average resting heart rate is about 70 bpm, this number can be derived through the following calculation:

$$\text{Stroke volume index } (\frac{\text{ml}}{\text{m}^2}) = \frac{\text{Cardiac index } (\frac{\frac{\text{mL}}{\text{min}}}{\text{m}^2})}{\text{Heart rate } (/\text{min})}$$

$$\textbf{Low flow state} = \frac{\mathbf{2500}}{\mathbf{70}} = \mathbf{35.7\ ml/m^2}$$

While the basis for this cutoff might be the minimum threshold for the cardiac index, it is noteworthy that in a normal population (from the Askelpios study by Rietzschel et al.) 31% of healthy individuals exhibited an

SVi of <35 ml/m² [178]. This indicates that an SVi of <35 ml/m² represents the physiological state of a significant portion of the population. Furthermore, in the population of 409 DLG-SAS patients with preserved function studied by Maor et al. [179], SVi was found to follow a normal distribution, with a mean of 39 ml/m². This indicates that more than half of the patients studied had SVi values of >35 ml/m². In their study, stroke volume, considered as a continuous variable, was found to be a strong predictor of cardiovascular events, whereas it was not significant when using the conventional cutoff of 35 ml/m² in a multivariate analysis that included age, sex, BMI, and LV mass index, as well as AVR as a time-dependent variable.

Other cutoffs have also been explored. For example, Eleid et al. [180] identified an increased mortality risk with a higher cutoff of 38 ml/m² in a cohort of 405 patients with DLG-SAS. Meanwhile, Rusinaru et al. [181], studied 1450 patients with an AVA of <1 cm² or an indexed AVA of <0.6 cm²/m². They ultimately proposed a threshold of 30 ml/m², demonstrating that mortality rates did not change significantly with higher values. A year later, the same 30 ml/m² cutoff was reused by the same research group for 983 patients with HG-SAS who were stratified based on this new threshold. The authors emphasized the importance of promptly referring these LF patients for valve replacement, irrespective of their symptom status [182]. Alternatively, the previously discussed research team of Maor et al. [179] proposed a threshold of 37 ml/m², while arguing that the risk of events increased continuously as SVi decreased when used as a continuous variable. Finally, the use of sex-specific thresholds (<40 ml/m² for men and <32 ml/m² for women) to define low-flow have been proposed so as to outperform the guidelines' threshold of 35 ml/m² in risk stratification following AVR [183].

Since the study by Hachicha et al., some studies have demonstrated that low-flow status is independently associated with a more advanced stage of the disease and lower survival [161,181,184-186], whereas other studies have found no association between flow status and survival [163,165]. Part of the explanation for these divergent results likely lies in the underlying cause of

the low-flow state. Clearly, having low forward flow due to inherently smaller ventricular volumes, as frequently seen in individuals of smaller stature, is fundamentally different from reduced flow resulting from an underlying cardiac condition. In fact, low-flow states are not only linked to left ventricular dysfunction but are also commonly associated with mitral regurgitation, mitral stenosis, tricuspid regurgitation, right ventricular dysfunction, and atrial fibrillation. Reduced arterial compliance (or increased valvulo-arterial impedance) and systemic hypertension also contribute to increased afterload, further reducing stroke volume [157,184].

There is an evident connection between low flow and low gradient, which contributes to discrepancies in severity classification. However, the prognostic impact of low flow remains inconsistent across studies. The 35 ml/m² cutoff appears inadequate for fully capturing the influence of low flow on patient survival. Additionally, the interplay between comorbidities and stroke volume complicates the establishment of a clear causal relationship.

3.4.2. Pressure recovery phenomenon

Measuring the diameter of the ascending aorta is essential to avoid potential underestimation of the AVA due to the pressure recovery phenomenon. As mentioned earlier, the MG obtained through echocardiography differs from the catheterization gradient because the measurements are taken at different levels, which does not account for the pressure recovery phenomenon. Consequently, the Doppler gradient and transvalvular aortic VTI can be overestimated. This issue is particularly important in patients with an aortic diameter at the sinotubular junction of <30 mm. In such cases, pressure recovery is more pronounced and must be systematically addressed during echocardiography by calculating the energy loss index [187]. Severe aortic stenosis is defined by an energy loss index < 0.6 cm²/m². A small aorta is often observed in patients with low body surface area, and

calculating the energy loss index often allows these cases of paradoxical LF/LG aortic stenosis to be reclassified as more moderate aortic stenosis [187].

3.4.3. Systemic resistances

An increase in valvulo-arterial impedance, resulting from reduced systemic arterial compliance and the development of arterial hypertension, is frequently observed in AS. These factors can contribute to the emergence of low-gradient discordant AS. Specifically, the rise in overall afterload (both valvular and arterial) can lead to a decrease in stroke volume, thereby lowering transvalvular pressure gradients. Additionally, the early reflection of arterial pressure waves during systole may further diminish these pressure gradients [157]. Consequently, an increase in systemic vascular resistance can account for a low gradient in patients with either normal or low flow. In patients with low-flow SAS, a calculated Zva of <4.5 mmHg/mL/m² provides insight into the underlying etiology of reduced stroke volume. Specifically, such a Zva value indicates that the diminished SV is unlikely to be due to excessive afterload, instead suggesting that intrinsic myocardial dysfunction is the primary cause [157].

3.4.1. Underlying amyloidosis

Growing evidence is emerging regarding the strong association between AS and cardiac amyloidosis (CA), particularly wild-type transthyretin (TTRwt). Identifying CA is particularly challenging in patients with AS because these two conditions have several features in common, with it being estimated that up to 15% of the AS population and up to 30% of those with a low-flow, low-gradient pattern may be afflicted by CA [188]. Disproportionate LV wall thickening and LV diastolic dysfunction relative to AS severity, RV wall thickening, pericardial effusion, bilateral atrial dilatation, impaired LV longitudinal systolic function, and a mitral annulus S' velocity ≤6 cm/s have

been demonstrated to be useful regarding the screening of CA in patients with AS and preserved LVEF [188].

In patients with AS, CA is associated with increased risks of heart failure, mortality, and treatment futility with aortic valve replacement [188]. Due to the shared phenotype and strong association between these conditions, CA certainly plays an underestimated role in the ongoing debate concerning the prognosis of DLG-SAS, which more frequently exhibits a low-flow state than HG-SAS.

3.5. Alternative perspectives

This section will explore the contribution of alternative imaging modalities, offering a different perspective on the current debate regarding the prognosis of DLG-SAS. The long-term progression of these patients, along with the presence of ongoing cardiac damage, will also be examined.

3.5.1. Calcification burden

The assessment of valvular calcification using CT imaging is currently recommended to differentiate between true severe and pseudo-severe stenosis in cases of low flow. Several studies have investigated this technique to better characterize DLG-SAS.

In 2013, Clavel et al. [189] studied 646 patients diagnosed with at least moderate AS and normal LVEF. The baseline evaluations included Doppler and CT imaging. Among the patients classified with DLG-SAS, only half displayed a high degree of valvular calcification. Furthermore, the study demonstrated that patients with DLG-SAS had significantly lower levels of aortic valve calcium compared to those with HG-SAS. Later, Kamperidis et al. [190] investigated 191 patients with severe aortic stenosis (AVAi <0.6 cm^2/m^2) and preserved LVEF. Their findings indicated no significant differences in aortic valve calcium load between the NFLG and LFLG groups, suggesting a relatively homogeneous calcium burden within these patient populations.

However, the calcium load was significantly lower than that observed in patients within the high-gradient group.

In 2021, Boulif et al. [108] provided concordant data by analyzing the aortic valve calcium (AVC) load in 266 patients with moderate to severe AS. They demonstrated that patients with discordant AS grading possessed a higher AVC load than those with moderate AS, but conversely had a lower AVC load than those with severe high-gradient AS. Similarly to the study conducted by Clavel et al., 36% to 55% of patients with DLG-SAS met the AVC load criteria for severe AS. Of particular note, among those patients with DLG-SAS, no differences in Agatston score, AVC density, or AVC index were found between those with NF and those with LF. While AVC load also predicted outcomes in these patients, its prognostic impact was less pronounced compared to those with concordant AS grading.

A recent ex vivo study by Pestiaux et al. utilized high-resolution micro-CT to provide a quantitative analysis of the structural characteristics of calcified cusps [191]. Their study revealed that the cusps in NFLG-SAS were less calcified compared to those in HG-SAS. Specifically, in HG-SAS, the primary calcified particles were found to be significantly larger and the initiation sites for calcification were more numerous, indicating a more active form of AS. Additionally, the thickness and volume of the NFLG-SAS cusps were significantly lower than those of HG-SAS.

A review of this data provides valuable insights, as, contrary to the echocardiographic findings, the literature on multidetector CT consistently indicates that DLG-SAS patients possess a lower calcium load when compared to HG-SAS patients [108,189-191].

3.5.2. Progression

Aortic stenosis is an inexorably dynamic process, with severity progressively worsening over time. However, the rate of progression can vary significantly

among individuals. We will now review global data on the progression of various entities to provide additional insights into this pathology.

Numerous studies have investigated the progression of DLG-SAS over time. The previously discussed study by Jander et al. [163] reported that 154 out of the 374 patients they examined (41%) with DLG-SAS progressed to HG-SAS over a median follow-up period of 46 months. Similarly, Maes et al. [160] demonstrated comparable findings after stratifying patients by flow: 82% of those with PLG-SAS experienced an increase in their mean transvalvular gradients over a median of 28 months, with half of them progressing to HG-SAS by the end of follow-up. Moreover, Triboulloy et al. [192] contributed to this topic, demonstrating that most patients with PLFLG-SAS and normal LVEF displayed a progressive increase in MG alongside a decrease in AVA over time, accompanied by mild LVEF impairment. Similar conclusions were also reported by Rezzoug et al. [165]: 11 out of the 16 patients (69%) with DLG-SAS continued to have DLG-SAS, but exhibited a significant increase in their mean pressure gradient. Meanwhile, the 5 remaining patients (31%) progressed to HG-SAS within two years following the initial evaluation.

More recently, a large study by Galian-Gay et al. investigated the changes in echocardiographic parameters over time in patients with PLFLG-SAS [193]. The study involved 903 patients with preserved left ventricular ejection fraction, stratified into high-gradient, normal-flow low-gradient (NFLG), and low-flow low-gradient (LFLG) groups. Notably, using a linear mixed model regression, the researchers found that the progression of the mean transvalvular gradient was similar between the LFLG and NFLG groups. During a median follow-up period of 60.2 months, among conservatively managed patients, 19.1% (n=9) of the LFLG group transitioned to NFLG AS, while 44.7% (n=21) progressed to HG-SAS. In patients undergoing aortic valve replacement, 58% (n=29) of those initially classified as LFLG ultimately underwent AVR with a diagnosis of HG-SAS. The authors concluded that the majority of patients with PLFLG-SAS evolve over time to other AS phenotypes, with most undergoing AVR classified as HG-SAS.

The data from these longitudinal studies on the progression of echocardiographic hemodynamic parameters unanimously indicate a progression of DLG-SAS toward a more severe high-gradient form.

3.5.3. Myocardial repercussions

This section focuses on myocardial remodeling and lesions detectable through cardiac magnetic resonance imaging (CMR). This approach aims to provide an indirect perspective on the severity of the different stages of AS by examining myocardial damage associated with increased wall stress and related pathological processes.

In 2013, Barone-Rochette et al. [(112)] compared the accuracy of echocardiographic measurements of LV hypertrophy and fibrosis across different types of AS using CMR. A total of 128 patients with an AVAi of <0.6 cm^2/m^2 and a LVEF of >50% underwent contrast-enhanced CMR. The study ultimately revealed significantly larger GOA in LFLG and NFLG as compared to LFHG-SAS. LV mass index was also lower in LFLG and NFLG than in LFHG SAS. Despite these differences, all AS groups displayed similar LV volumes, predominantly concentric hypertrophic remodeling, along with comparable amounts of focal myocardial fibrosis.

These findings were further corroborated by Slimani et al. [(194)], who analyzed left ventricular geometry, longitudinal function, and fibrosis in a cohort of 147 patients with moderate-to-severe aortic stenosis and normal left ventricular ejection fraction, alongside 75 healthy controls. Their study revealed that patients with DLG-SAS were less likely to exhibit reduced longitudinal deformation, LV hypertrophy, or myocardial fibrosis compared to those with HG-SAS. Additionally, they concluded that interstitial fibrosis occurs only when reduced longitudinal deformation and severe HG-AS are both present.

Similar to the findings concerning calcification burden and the progression of hemodynamic parameters over time, the MRI data supports a lower degree of myocardial remodeling and fibrosis in cases of discordance between AVA/MG compared to HG-SAS patients. These results position DLG-SAS patients at an intermediate stage within the disease spectrum.

Part 4. TIMING FOR VALVE REPLACEMENT: THE DEBATE

4.1. Overview

Aortic valve replacement remains the only intervention that improves prognosis [142,154], as there are currently no effective pharmacological treatments available. However, the benefits of AVR must be carefully balanced against procedural risks and the long-term complications associated with valve substitutes, including their limited durability. Therefore, careful patient selection and optimal timing of the procedure are essential to maximize the benefits of AVR. At present, valve replacement is indicated solely for patients with severe stenosis. Consequently, the initial step in selecting candidates for the procedure is to confirm the severity of the disease. In cases of uncertainty, multimodal imaging plays a crucial role in differentiating true severe stenosis from pseudo-severe forms, as outlined in the preceding chapters.

The presence of symptoms attributable to the disease plays a crucial role in the decision-making process. This is because their onset marks a pivotal point in the natural history of the disease, as it is associated with poor short-term prognoses [3]. Therefore, symptoms provide a strong indication for intervention [4,5]. The decision of whether and when to intervene in asymptomatic severe AS in order to improve overall outcomes remains a subject of debate [195,196]. However, this is not the case in specific high-risk scenarios recognized as interventional indications [4,5] , which will be elaborated on further.

4.1.1. Guideline triggers

Based on the previous discussions above, current guidelines categorize patients according to their symptomatic status (**Figure 33**). Symptomatic patients with HG-SAS or classical LFLG-SAS (LVEF <50%) with flow reserve are assigned a Class I recommendation for AVR. In contrast, patients with

PLFLG-SAS or classical LFLG-SAS without flow reserve qualify for intervention only if they are symptomatic and the severity of stenosis is confirmed (e.g., through the use of calcium scoring), which corresponds to a Class IIa recommendation.

In asymptomatic patients, two types of situations also prompt AVR as a Class I recommendation:

- Patients with systolic left ventricular dysfunction, defined as an ejection fraction <50% when there are no other identifiable causes (Class IB) [9,197,198].
- Pseudo-asymptomatic patients, where exercise testing reveals functional limitations attributable to AS (Class IC).

Guidelines also recommend that intervention should be considered in the following patient groups:

- Patients with mildly reduced systolic left ventricular dysfunction: LVEF <55%, with no other identifiable causes (Class IIaB) [156].
- Patients with a sustained drop in blood pressure >20 mmHg during exercise testing (Class IIaC).
- Patients with LVEF >55% and normal exercise test results, who are at low procedural risk and meet one or more of the following criteria (Class IIaB):
    - Mean gradient ≥60 mmHg or peak velocity >5 m/s [199].
    - Severe valve calcification with a peak velocity progression ≥0.3 m/s/year [200,201].
    - B-type natriuretic peptide (BNP) levels >3× the age- and sex-corrected normal range, confirmed by repeated measurements and without any alternative explanations [202,203].

A) Symptomatic aortic stenosis	Class[b]	Level[c]
Intervention is recommended in symptomatic patients with severe, high-gradient aortic stenosis [mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, and valve area ≤1.0 cm^2 (or ≤0.6 cm^2/m^2)].[235,236]	I	B
Intervention is recommended in symptomatic patients with severe low-flow (SVi ≤35 mL/m^2), low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction (<50%), and evidence of flow (contractile) reserve.[32,237]	I	B
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) aortic stenosis with normal ejection fraction after careful confirmation that the aortic stenosis is severe[d] (*Figure 3*).	IIa	C
Intervention should be considered in symptomatic patients with low-flow, low-gradient severe aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CCT calcium scoring confirms severe aortic stenosis.	IIa	C
Intervention is not recommended in patients with severe comorbidities when the intervention is unlikely to improve quality of life or prolong survival >1 year.	III	C

B) Asymptomatic patients with severe aortic stenosis	Class[b]	Level[c]
Intervention is recommended in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) without another cause.[9,238,239]	I	B
Intervention is recommended in asymptomatic patients with severe aortic stenosis and demonstrable symptoms on exercise testing.	I	C
Intervention should be considered in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <55%) without another cause.[9,240,241]	IIa	B
Intervention should be considered in asymptomatic patients with severe aortic stenosis and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C
Intervention should be considered in asymptomatic patients with LVEF >55% and a normal exercise test if the procedural risk is low and one of the following parameters is present: • Very severe aortic stenosis (mean gradient ≥60 mmHg or V_{max} >5 m/s).[9,242] • Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year.[164,189,243] • Markedly elevated BNP levels (>3× age- and sex-corrected normal range) confirmed by repeated measurements and without other explanation.[163,171]	IIa	B

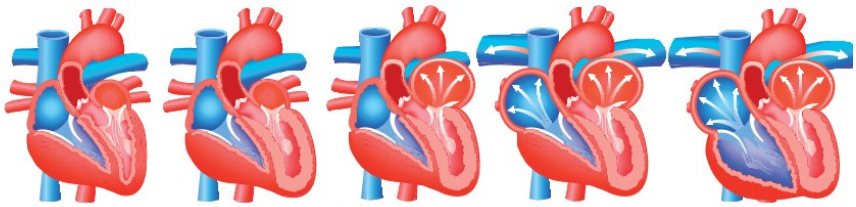
Figure 33: ESC/EACTS Guidelines recommendations on indications for intervention in symptomatic (A) and asymptomatic (B) aortic stenosis. From Vahanian et al. Eur Heart J. 2021.

4.1.2. Prognostic parameters

In addition to the operative criteria outlined in the guidelines, other predictors of poor prognosis have been identified in the literature.

These include clinical characteristics such as older age, atherosclerotic risk factors, and echocardiographic parameters such as: severe LV hypertrophy **(204)**, low stroke volume index **(181)**, increased left atrial volume **(11)** and/or pulmonary hypertension **(205)**, reduced LV global longitudinal strain **(100,101)**, and abnormal biomarker levels (natriuretic peptides, troponin, and fetuin-A) **(202,203,206,207)**. However, these markers have not yet led to specific recommendations for AVR.

Another interesting point of view was introduced by Généreux et al. [208], who proposed a staging classification for AS based on the extent of cardiac damage, providing a framework for risk stratification and guiding treatment decisions. The system comprises five stages: Stage 0 (no cardiac damage), Stage 1 (left ventricular damage, including hypertrophy or diastolic dysfunction), Stage 2 (left atrial or mitral valve damage), Stage 3 (pulmonary vasculature and tricuspid valve damage), and Stage 4 (right ventricular damage) (**Figure 34**). Each stage represents progressive disease severity and is correlated with increasing mortality risk. Advanced stages (3 and 4) are associated with poor outcomes even after AVR, highlighting the necessity of timely intervention. This classification emphasizes the systemic effects of AS, extending beyond the valve to encompass broader cardiac dysfunction. It advocates for earlier AVR in select patients, including those with borderline or asymptomatic presentations, to avert irreversible damage.



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

Figure 34: Staging of aortic stenosis based on the extent of cardiac damage. LA, left atrial; LV, left ventricular; RV, right ventricular. From Généreux et al. Eur Heart J 2017;38:3351-3358 [208].

4.2. Class I triggers: pitfalls

According to the 2019 VHD II survey [34], Class I triggers are the primary indications for AVR in patients with severe aortic stenosis (MG >40 mmHg). While these Class I criteria are widely recognized as strong justifications for valve replacement, an increasing body of evidence questions whether they may be too late, potentially resulting in delayed treatment with prognostic implications. The subsequent chapters delve deeper into the issues highlighted by these studies.

4.2.1. Symptoms

Asymptomatic patients with severe aortic stenosis, defined by a peak velocity > 4 m/s, appear to have survival rates comparable to the age- and sex-matched general population for several years [10,209]. In contrast, patients who develop symptoms experience a dramatic decline in prognosis, with a 50% mortality rate at three years without intervention [3] and possibly altered outcomes, even after AVR [8,154]. Indeed, Kvidal et al. [154] demonstrated that patients with SAS undergoing AVR in NYHA functional Class III or IV had excess postoperative mortality rates of 20% and 32% at 10 and 15 years, respectively. Conversely, patients operated on in functional Class II, had similar survival than the corresponding group in the general population. Additionally, Pierard et al. [8] also examined the impact of preoperative symptoms on postoperative survival, finding that being in NYHA functional Classes III or IV was an independent predictor of both short- and long-term postoperative mortality. This risk was further heightened in cases where symptom deterioration was rapid prior to AVR. As noted in the previous study, asymptomatic patients or those with mild symptoms (NYHA 2) demonstrated a survival rate comparable to that of the general population at seven years.

In summary, the absence or presence of symptoms profoundly influences patient prognosis. However, the distinction between the two is not always

clear-cut. Many patients, particularly the elderly, are often pseudo-asymptomatic [210]. The detection of symptoms during consultation largely relies on the patient's subjective reporting of their experiences. However, in chronic conditions, patients often develop a form of habituation to their symptoms, adapting their behavior to avoid functional limitations. Additionally, some patients may intentionally downplay or deny symptoms out of fear or anxiety regarding potential interventions. When patients present additional comorbidities (e.g., pulmonary disease, chronic kidney disease, obesity), it can be challenging to determine the extent to which symptoms are attributable to VHD. Furthermore, follow-up consultations every 3 to 6 months may be insufficient or poorly timed, leading to delays in diagnosis and management. Indeed, 20% of patients with severe aortic stenosis will develop symptoms within a year, and 80% within three years [201]. For these reasons, both European and American guidelines recommend systematically performing exercise testing to reveal hidden symptoms [4,5].

A supervised stress test can unmask symptoms, especially when repeated every 3 to 6 months in order to detect changes compared to the baseline exam. Despite its theoretical advantages, it is performed in only a small subset of eligible patients, typically younger individuals without orthopedic or neurological issues—characteristics that do not necessarily represent the typical age or profile of the AS population [211]. The VHD survey highlighted this underutilization in routine practice, reporting that fewer than 10% of patients underwent the test [34]. Additionally, the predictive ability of exercise testing for symptom onset and outcomes within one year is limited, with a positive predictive value of only 55% to 65%, based on small patient cohorts [211,212].

Finally, it is concerning that, despite systematic follow-up and the availability of exercise testing, 48% of patients referred for AVR already presented severe symptoms, and 12% required hospitalization for acute heart failure [34]. These findings highlight a delay in symptom management, emphasizing the need for improvement in early detection and intervention.

4.2.2. Left ventricle dysfunction

Left ventricular ejection fraction is commonly used as a surrogate marker for LV systolic function, despite its limitation due to load dependence. The current guideline threshold for defining LV dysfunction is an LVEF of <50%. However, in recent years, several studies have questioned this threshold, suggesting more conservative cutoffs, as post-operative mortality significantly increases when pre-operative LVEF drops below 55% [156] or even 60% [9,198,213]. These studies have led the European guidelines to recommend AVR as a Class IIa indication for asymptomatic patients with LVEF <55% [5]. Similarly, the American guidelines suggest AVR as a Class IIb indication for patients with HG-SAS if there is a progressive decline in LVEF to <60% across three separate evaluations [4].

From a pathophysiological perspective, as AS progresses, the LV hypertrophies to minimize wall stress. Over time, this LV remodeling becomes maladaptive, leading to structural changes and a gradual decline in LVEF. Consequently, LVEF may appear preserved despite underlying reduced contractility and therefore fails to accurately reflect the ongoing subclinical cardiac damage.

Several studies have investigated these subclinical changes in the LV myocardium. The meta-analysis conducted by Magne et al. [100] demonstrated that among 1067 asymptomatic patients with moderate-to-severe AS and LVEF >50%, a significant proportion already exhibited abnormal LV longitudinal strain (GLS <20%). Patients with global GLS <14.7% had more than a 2.5-fold increased risk of mortality despite apparently normal LVEF. The authors attribute this reduction in GLS to progressive tissue fibrosis and emphasize its subsequent prognostic significance. In a multicenter observational study of 674 patients with severe AS undergoing AVR, Musa et al. [117] demonstrated that late gadolinium enhancement (LGE) was independently associated with all-cause mortality, regardless of LVEF.

Each 1% increase in LV myocardial scarring, as detected by LGE CMR, was linked to an 11% higher risk of all-cause mortality and an 8% higher risk of cardiovascular mortality.

All of these findings raise the question of the relevance of waiting for a decline in LV function, as evidenced from the various remodeling markers that indicate irreversible myocardial damage occurs early in the disease process. LV dysfunction defined by an LVEF of <50% appears to occur very late in AS' natural history, and at this stage, patients are rarely asymptomatic [(214)]. Consequently, identifying structural myocardial changes is crucial, as they develop before LVEF declines, can persist after AVR, and are independently associated with poor outcomes [(100,117)].

4.3. Early replacement vs watchful waiting: the debate

The current guidelines for the management of severe VHD primarily determine the timing for AVR based on the onset of symptoms or a decline in LV function. However, as previously outlined, these indications, although strongly supported by robust data, have notable limitations. With an increasing body of evidence suggesting a potential prognostic impact of delaying intervention until criteria emerge late in the disease course, the question of early treatment in asymptomatic patients has become pertinent. Consequently, the discourse has shifted toward considering a preemptive AVR approach rather than a wait-and-see strategy.

The relationship between early intervention and outcome has already been explored by several research groups. Currently, three randomized controlled trials (RCTs) and several observational studies have sought to contribute to the ongoing debate.

The **CURRENT AS** registry is a large-scale multicenter observational study that included 1808 consecutive asymptomatic patients with HG severe AS, of whom 291 underwent early AVR and 1517 were managed conservatively

[197]. Using a propensity score matching approach to account for potential confounders, the researchers selected two subgroups of 291 patients each. The results of this study support an initial AVR strategy, demonstrating reduced mortality and fewer hospitalizations for heart failure compared to a conservative approach.

The first randomized trial, **RECOVERY**, conducted in Korea, was published in 2019. It randomized 73 patients to early surgery and 72 to a conservative management strategy [215]. The inclusion criteria indicated a more severe degree of AS than is typically employed, with an AVA of ≤ 0.75 cm^2 and a Vmax of ≥ 4.5 m/s or a mean gradient of ≥ 50 mmHg. The study population was relatively youthful, with a mean age of 64 years and characterized by a low surgical risk, as evidenced by a median EuroSCORE II of 0.9%. Absence of symptoms was determined through patient history, and exercise testing was conducted only in cases where symptoms were questionable. The primary outcome of operative or postoperative cardiovascular mortality was significantly better in the early surgery group compared to the conservative management group. The advantage of early surgery was consistent across secondary endpoints, including all-cause mortality. However, this study has been a topic of debate in the literature due to its inclusion criteria, which do not reflect common clinical practice. It focused on young, low-risk patients with very severe AS, of whom 60% had bicuspid aortic valves and 6% had rheumatic disease.

The second randomized trial, **AVATAR**, included patients meeting conventional criteria for severe AS (AVA ≤ 1.0 cm^2 and Vmax ≥ 4.0 m/s or mean gradient ≥ 40mmHg) [216]. A key strength of this study was the systematic use of exercise testing to confirm the absence of symptoms. However, the study population was still relatively young (mean age 67 years-old) with a low surgical risk (median STS score of 1.7%). Patients were randomized and assigned to one of two groups: 78 patients to early surgery, and 79 to a conservative strategy. The primary composite endpoint, which included all-cause mortality and major adverse cardiac events, was

significantly lower in the early AVR group compared to the conservative management group. Notably, there was no difference in all-cause mortality between the groups. However, there was a trend toward fewer hospitalizations for heart failure in the early surgery group. The authors further examined the lack of a mortality difference, emphasizing the challenge of systematically determining the precise cause of death. They reported that among the 16 deaths in the conservative strategy group, four were attributed to pneumonia, including three due to COVID-19. While the AVATAR study yielded less striking results than RECOVERY and employed a conventional definition of severe AS, its findings should be interpreted with caution due to the exclusion of patients with common comorbidities or high surgical risk.

A recent meta-analysis (2023) conducted by the Portuguese team led by Costa et al., which combined data from 10 studies (two prospectives and eight retrospectives) along with the two randomized trials, including a total of 4130 patients [(217)]. The overall effect revealed a significant association between early AVR and reduced all-cause mortality compared to conservative management.

Very recently (October 2024), a third randomized controlled trial (RCT), **EARLY TAVR**, was published on the topic, this time including a large cohort of asymptomatic patients (90% with negative treadmill stress tests) [(218)]. A total of 901 patients were randomized to either immediate TAVR or conventional follow-up, with a higher mean age (75 years) compared to other studies, yet maintained a low-risk profile (median STS score of 1.6%). A clear benefit was demonstrated for the primary endpoint, which encompassed all-cause mortality, stroke, and unplanned cardiovascular hospitalizations. However, an analysis of the individual components of the primary endpoint indicated no significant differences in mortality or stroke alone, which is consistent with the findings of the AVATAR trial. Thus, the observed benefit in the primary endpoint was primarily driven by unplanned hospitalizations. Notably, these hospitalizations occurred twice as

frequently in the conservative group (41.7% vs. 20.9%), largely influenced by the endpoint design, as the authors classified AVR performed during conservative follow-up as an unplanned hospitalization. The early and high rates of symptom onset and conversion to TAVR in patients who previously underwent treadmill stress testing raise significant concerns regarding the rapid progression of the disease and the limited reassurance afforded by a negative test. This situation prompts questions about the adequacy of clinical follow-up and the reliability of treadmill stress testing in predicting short-term symptom development within this population.

In summary, the current body of evidence supports the benefits of an early interventional strategy in asymptomatic patients, though with some caution. However, data from RCTs involving less selective patient profiles are still lacking, making it difficult to draw definitive conclusions or revise current guidelines. In this regard, several studies are currently underway and will provide useful information in determining the optimal timing for AVR: ESTIMATE (Early Surgery for Patients with Asymptomatic Aortic Stenosis—NCT02627391), EVOLVED (Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Patients with Asymptomatic Severe Aortic Stenosis—NCT03094143), DANAVR (Danish National Randomized Study on Early Aortic Valve Replacement in Patients with Asymptomatic Severe Aortic Stenosis—NCT03972644), and EASY-AS (Early Valve Replacement in Severe, Asymptomatic Aortic Stenosis Study—NCT04204915).

Part 5. AIMS OF THE THESIS AND HYPOTHESES

The general aim of this thesis was to provide a comprehensive overview of the management of aortic stenosis, addressing three ongoing debates: the true severity of low-gradient discordant stenoses, the optimal timing for interventional treatment in asymptomatic patients, and the impact of atrial fibrillation on AS. Furthermore, in the era of increasingly personalized medicine, we conducted an ex vivo study of the uptake of a bone-specific PET/CT tracer on aortic valves with varying degrees of severity. This tracer was evaluated as a potential novel marker of calcific activity, which, according to the literature, is associated with the risk of disease progression and cardiovascular events. We also aimed to demonstrate for the first time that aortic valve microcalcifications could be visualized using nano-CT imaging (with a resolution of around 5-15 microns). Our goal was to demonstrate that NaF binds preferentially in these areas of microcalcification, thereby supporting its use in clinical studies assessing AS progression.

<u>To achieve these goals:</u>

The first study focused on comparing the prognostic relevance of severity discordances among echocardiographic parameters. This was accomplished using pseudo-randomization techniques, including inverse propensity weighting and propensity score matching, to generate the most comparable groups possible from a heterogeneous population with a high burden of comorbidities.

This study was entitled “Prognostic Implications of Discordant Low-Gradient Severe Aortic Stenosis Comprehensive Analysis of a Large Multicenter Registry”, and its purpose was to compare the outcome of patients with either moderate AS, discordant low gradient severe AS, or high gradient severe AS after matching baseline characteristics.

We hypothesized that DLG-SAS represents an intermediate form of AS in the disease spectrum, between MAS and HG-SAS.

The second study analyzed post-operative survival in patients based on the type of operative trigger identified retrospectively. Patient survival was adjusted for confounding factors and compared to the survival rates of the general population of the same age and sex.

This study was entitled "Quantifying the Survival Loss Linked to Late Therapeutic Indication in High-Gradient Severe Aortic Stenosis," and its purposes were:

- To explore the impact of guideline-based Class I triggers on late post-operative survival rates in HGSAS patients.
- To evaluate whether patients operated on without Class I triggers can achieve a restored normal life expectancy comparable to that of the general population.
- To evaluate the impact of different pre-operative LVEF thresholds on late post-operative survival.
- To quantify the 10-year survival loss linked to Class I triggers.

We hypothesized that the current Class I interventional criteria are met too late in the course of the disease, negatively affecting the long-term prognosis of patients.

The **third study** investigated the impact of atrial fibrillation on clinical outcomes in patients with SAS with preserved left ventricular ejection fraction (LVEF ≥50%) compared with sinus rhythm. These included AVR rates, determinants of overall mortality, and the determinants of referral for treatment.

This study was entitled "Atrial fibrillation in severe aortic stenosis: Impact on patient's mortality and referral to treatment".

We hypothesized that AF, compared with SR, is associated with an increased risk of mortality in SAS patients with preserved LVEF, independently of AS-induced cardiac remodeling. Furthermore, we hypothesized that AVR is beneficial for all SAS patients, regardless of atrial rhythm and symptom status, and that AF patients with SAS and a preserved ejection fraction are often under-referred for AVR, despite presenting with a higher burden of symptoms.

The **prospective "ex vivo" experimentation** primarily involved multimodal imaging (microPET, microCT, high-resolution nanoCT, and histology) on aortic valve specimens obtained from the surgical program and homografts deemed unsuitable for implantation. This study focused on utilizing the 18F-NaF PET/CT tracer as a surrogate marker of calcific activity. The objectives of this experiment were:

- To develop a reproducible methodology for using this tracer.
- To demonstrate the selectivity of the tracer through epitope saturation (blocking).
- To confirm the presence of microcalcification utilizing especially high-resolution imaging and correlate it with tracer uptake.
- To evaluate patterns or "mismatches" between tracer uptake and calcification burden.

We hypothesized a nonlinear relationship between tracer uptake and calcification burden, suggesting that signal intensity is not merely proportional to the total calcium deposit load, but rather depends on the distribution of microcalcifications throughout the valve.

Part 6. THESIS STUDIES

This section presents the four main studies that form the body of this thesis:

6.1. STUDY 1: Prognostic Implications of Discordant Low-Gradient Severe Aortic Stenosis Comprehensive Analysis of a Large Multicenter Registry.

Published in: JACC: ADVANCES, 2023, VOL. 2, NO. 2.

6.2. STUDY 2: Quantifying the Survival Loss Linked to Late Therapeutic Indication in High-Gradient Severe Aortic Stenosis.

Published in: JACC: ADVANCES, 2024, VOL. 3, NO. 3.

6.3. STUDY 3: Atrial fibrillation in severe aortic stenosis: Impact on patients' mortality and referral to treatment.

Unpublished.

6.4. EXPERIMENTAL STUDY: "Ex Vivo" 18F-NaF Uptake, a Surrogate Marker of Calcific Activity in Aortic Valve Stenosis.

Unpublished.

6.1. STUDY 1: Prognostic Implications of Discordant Low-Gradient Severe Aortic Stenosis Comprehensive Analysis of a Large Multicenter Registry

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ABSTRACT

OBJECTIVE. Up-to-30% of patients with severe aortic stenosis (SAS) (indexed aortic valve area [AVAi] < 0.6 cm2/m2) exhibit low-transvalvular gradient despite normal ejection fraction. There is intense debate regarding the prognostic significance of this entity. To compare the outcome of patients with discordant low-gradient SAS (DLG-SAS) vs moderate aortic stenosis (MAS) and high-gradient SAS (HG-SAS).

METHODS. We used the BEL-F-ASt (Belgium-France-Aortic Stenosis) registry including consecutive patients with AS. Survival was compared overall and after matching (inverse probability weighting and propensity-score matching) for clinical and imaging variables. The analysis was first performed in the overall population (n ¼ 2,582) and then in the population of unoperated patients (n = 1,812).

RESULTS. After-inverse probability weighting-matching, the 3 groups were balanced. Five-year survival was better in MAS than in DLG-SAS and HG-SAS-patients (58.9% vs 47% vs 41.2%, P<0.001). Similar results were obtained in unoperated patients (54.1% vs 37.9% vs 28.1%, P<0.001). To explore the impact of MG (≤40 vs >40 mmHg) and AVAi (<0.6 vs ≥0.6 cm^2/m^2) on outcomes, survival of propensity score-matched cohorts of HG-vs DLG-SAS and MAS vs DLG-SAS were compared. After matching for MG, survival was better in MAS than in DLG-SAS (52% vs 40%, P<0.001). After matching for AVAi, survival was better in DLG-SAS than in HG-SAS patients (45% vs 33%, P < 0.001).

CONCLUSIONS. Survival of DLG-SAS is better than that of HG-SAS and worse than that of MAS patients. At comparable MG, the lower the AVAi, the worse the prognosis, whereas at comparable AVAi, the higher the MG, the worse the prognosis. These data argue that DLG-SAS is an intermediate form in the disease continuum.

1. INTRODUCTION

Aortic valve stenosis (AS) is the most prevalent valvular disease in the Western world, affecting more than 5% of patients aged over 65 years [(1)]. Echocardiography is the gold standard for assessing AS severity. Severe aortic stenosis (SAS) in its typical form, that is, high-gradient SAS (HG-SAS), is defined as an aortic valve area (AVA) <1.0 cm^2 or an indexed AVA (AVAi) <0.6 cm^2/m^2 and a mean gradient (MG) >40 mmHg [(4,5)]. However, 10 to 30% of patients present with discordant findings: lower-than-expected peak transvalvular velocities and mean pressure gradients (MG ≤40 mmHg) despite SAS based on AVAi (<0.6 cm^2/m^2). Since transvalvular pressure gradients are flow-dependent, it has long been admitted that patients with left ventricular (LV) dysfunction and low cardiac output may present with low MG despite SAS [(6)]. More recently, retrospective studies have shown that such low transvalvular gradients can also be observed in patients with preserved LV ejection fraction (LVEF) [(95,97)], presumably as a result of small cavity sizes and low stroke volumes, typically <35 mL/m^2. Because it is observed in patients with normal LVEF, this subset of SAS has been termed "discordant low-gradient" (DLG-SAS). Clearly, this situation raises uncertainty regarding the actual severity of the stenosis, prognostic implications, and therapeutic management. Indeed, some authors consider this entity as a more advanced form of AS [(158)], with increased interstitial fibrosis [(219)], reduced LV longitudinal function [(98)], and poor prognosis under conservative treatment [(99)], while others provided evidence that it is a more benign form of AS, with an outcome similar to that of moderate AS (MAS) [(159,160)]. In addition, it has been found out that DLG-SAS patients are "en route" toward the more severe HG-SAS, since the majority of them experience a MG increase over time [(160)]. Consistently, magnetic resonance imaging data in DLG-SAS show larger AVAs, less hypertrophy, and similar focal fibrosis compared to HG-SAS [(112)]. Survival analyses of limited patient numbers suggest that DLG-SAS is associated with a greater mortality risk than HG-SAS [(99)], while it was more recently shown that the outcome of DLG-SAS was similar to that of MAS and was not favorably influenced by aortic

valve surgery [159,163]. All these conflicting data raise questions about the real severity of DLG-SAS, and a better comprehension of this particular entity should help clinicians in making appropriate therapeutic decisions. Indeed, current guidelines mention that treatment may be considered in symptomatic patients with DLG-SAS, but only as a class IIa indication (level of evidence C), which reflects the uncertainty as to treatment survival benefit [4].

In view of these controversies and given the lack of randomized trials, the only option for refining the prognostic implication of DLG-SAS is to gather registries of patients with SAS and to compare the outcome after matching baseline characteristics. In this work, we gathered large and well-defined AS registries (treated and untreated patients) in France and Belgium and hypothesized that DLG-SAS represents an intermediate form of AS in the disease continuum, between MAS and HG-SAS. By censoring patients at the time of surgery, we sought to minimize the effects on outcome of treatment and of its potentially heterogeneous use in the 3 groups.

2. METHODS

STUDY POPULATION AND DESIGN. Patients aged 18 years and older, who were diagnosed with at least mild AS in the echocardiography laboratories of 2 French (Amiens and Lille) and one Belgian (Brussels) tertiary hospitals between 2000 and 2020, were prospectively enrolled and entered in an electronic database (**Figure 1**). Exclusion criteria were as follows: 1) AVAi >0.85 cm^2/m^2, 2) previous valvular surgery, congenital heart disease, subvalvular aortic stenosis, or dynamic LV outflow tract (LVOT) obstruction, 3) more than mild aortic or mitral regurgitation, 4) LVEF <50%, 5) glomerular filtration rate <30 mL/min, 6) patients without any follow-up (inclusion date = last follow-up date), 7) patients operated on within the first 3 months following the inclusion date, and 8) refusal to participate in the study. Overall, we enrolled 2,582 patients of which 1,812 were medically managed. The patients were retrospectively classified into 3 groups: MAS (AVAi ≥ 0.6

cm^2/m^2, MG ≤ 40 mmHg, n = 876), DLG-SAS (AVAi < 0.6 cm^2/m^2, MG ≤ 40 mmHg, n = 933), and HG-SAS (MG > 40 mmHg, AVAi < 0.6 cm^2/m^2, n = 773). The validated Charlson comorbidity index was calculated for each patient [220]. Coronary artery disease (CAD) was defined as the presence of a documented history of acute coronary syndrome, CAD previously confirmed by coronary angiography, or history of coronary revascularization. Symptoms were ascertained by each patient's personal cardiologist and graded according to the New York Heart association (NYHA). The study was conducted in accordance with institutional policies and the revised Helsinki Declaration.

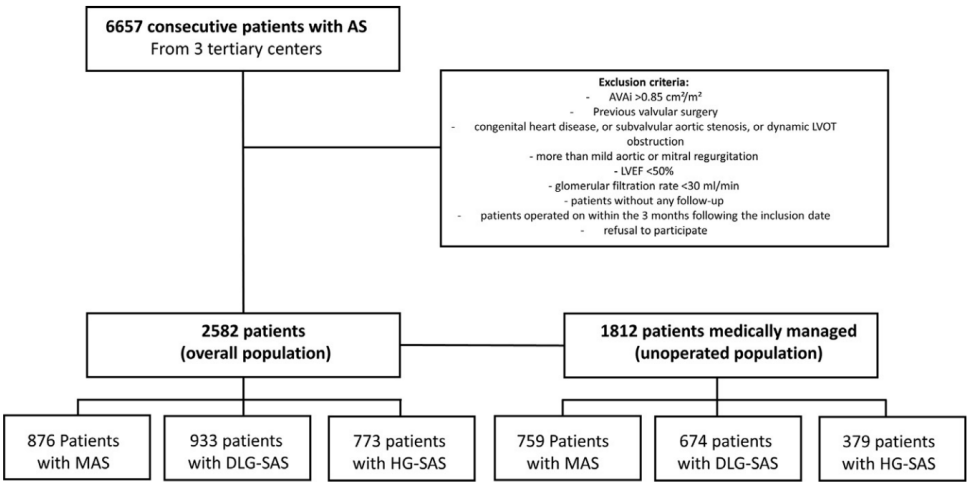


Figure 1: Flow Chart Illustrating Case Selection and Classification. AVAi = indexed aortic valve area; DLG-SAS = discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis; LVEF = left ventricular ejection fraction; MAS = moderate aortic stenosis.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive ultrasound examination using commercially available systems, including 2-dimensional echocardiography as well as Doppler examinations. Multiple transducer positions were systematically used to record maximal instantaneous and

mean pressure gradients across the aortic valve. AVA was calculated by the continuity equation and indexed for body surface area (BSA). In patients with atrial fibrillation, 5 consecutive beats were systematically averaged. LV volumes and LVEF were calculated by using the biplane Simpson method. LV stroke volume was calculated by means of the LVOT area on the parasternal long-axis view multiplied by the LVOT velocity–time integral measured by pulsed-wave Doppler. Systolic pulmonary artery pressure was estimated by measuring the systolic transtricuspid pressure gradient, as calculated using the modified Bernoulli equation.

FOLLOW-UP AND OUTCOME. As previously reported [182], initial treatment after the index evaluation was either conservative or surgical, as judged appropriate by the patient's cardiologist. Subsequent clinical decisions about surgical management (aortic valve replacement [AVR]) were made by the heart team with the approval of the patient's personal physician, as per guidelines. Clinical follow-up data were obtained by direct patient interview and telephone calls to physicians, patients, or their relatives if necessary. Follow-up started at the time of the index echocardiography, and patients undergoing AVR during follow-up were censored at the time of surgery. The study endpoint was overall mortality.

STATISTICAL ANALYSIS. Continuous data are expressed as mean ± standard deviation or median and interquartile range [IQR], depending on distribution normality. Categorical data are expressed as number and percentage. The differences in baseline continuous data among the 3 groups were explored using one-way analysis of variance (for normally distributed data) or Kruskal-Wallis test (for nonnormally distributed data). Pearson's chi-squared test was used for categorical variables. Outcomes are displayed using the Kaplan-Meier method and were compared using 2-sided log-rank tests. Multivariable analyses of all-cause mortality were performed using Cox proportional hazards models adjusted for baseline characteristics. In order to avoid bias related to surgical treatment, these analyses were conducted both on the overall population of 2512 patients and on the specific

population of 1812 unoperated patients. To adjust for covariates between groups (MAS, DLG-SAS, and HG-SAS), a propensity score inverse probability weighting (IPW) estimation was computed for each patient. All baseline characteristics that were significantly different between groups with a prognostic impact in multivariate analysis by Cox survival model (**Tables 1 and 2**) were used to calculate the propensity score IPW for each patient. The 5-year overall survival, computed using the Kaplan-Meier method adjusted for inverse probability weights, was then determined in order to clarify the impact of AS groups. Weighted groups were compared using log-rank chi-squared tests. The proportional hazards assumption was confirmed using statistics and graphs based on Schoenfeld residuals.

Finally, to explore the impact of MG (≤40 mmHg vs >40 mmHg) in patients with an AVAi <0.6 cm^2/m^2 (DLG-SAS vs HG-SAS) and of AVAi (<0.6 cm^2/m^2 vs ≥0.6 cm^2/m^2) in patients with a MG ≤ 40 mmHg (DLG-SAS vs MAS), we performed 2 different propensity score matching analyses. First, we added the MG to clinical variables for generating a propensity score for each patient with an AVAi <0.6 cm^2/m^2. Matched patient pairs (DLG-SAS vs HG-SAS) were then compared and 5-year overall survival analysis using the Kaplan-Meier method was carried out. Secondly, we added the AVAi to clinical variables for generating a propensity score for each patient with a MG ≤40 mmHg. Survival of matched patient pairs (MAS vs DLG-SAS) was compared as well. Propensity score matching was performed separately in the overall population and in the population of unoperated patients. All statistical analyses were conducted using the RStudio 1.4.1106 (ipw and weights packages) [221] and the SPSS version27.0(IBMCorp, Armonk, NY) software. A P-value of <0.05 was considered statistically significant.

3. RESULTS

BASELINE CHARACTERISTICS. The overall population consisted of 2582 patients, of which 876 (34%) presented with MAS, 933 (36%) with DLG-SAS, and 773 (30%) with HG-SAS (**Table 1**). DLG-SAS patients were older and more frequently had diabetes and atrial fibrillation, as well as lowered stroke volume index and increased systolic pulmonary arterial pressure. MAS patients were less often in NYHA class >2 and had the highest LVEF. HG-SAS patients had more severe symptoms according to NYHA classification and more often grade 2 aortic regurgitation. There was no significant difference between groups in other clinical parameters, such as sex, angina, syncope, hypertension, and CAD. The Charlson comorbidity index was similar between the 3 groups. After IPW, no significant difference in baseline characteristics persisted (**Table 1, right column**).

Table 1: Baseline and inverse probability weighting (IPW)-weighted characteristics of the overall population.

	Overall Population (n = 2,582)				IPW Population			
	MAS N = 876	DLG-SAS N = 933	HG-SAS N = 773	*P*-Value	MAS N = 876	DLG-SAS N = 933	HG-SAS N = 773	*P*-Value
Clinical data								
Male sex (n, %)	468 (53.4)	454 (48.7)	400 (51.7)	0.12	50.9%	50.5%	51.2%	0.97
Age (y)	76 ± 11	77 ± 11	76 ± 12	0.001	76 ± 11	77 ± 11	77 ± 11	0.88
BMI (kg/m^2)	27 ± 5	28 ± 6	28 ± 5	0.001	28 ± 6	28 ± 5	28 ± 5	0.60
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.002	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.90
NYHA I/II (n, %)	796 (91)	735 (78.8)	584 (75.5)	<0.001	80.1%	81.4%	81.8%	0.81
Angina (n, %)	121 (13.8)	131 (14.0)	129 (16.7)	0.19	14.7%	13.5%	15.5%	0.68
Syncope (n, %)	56 (6.4)	54 (5.8)	61 (7.9)	0.21	5.5%	5.9%	8.6%	0.16
Diabetes (n, %)	273 (31.2)	314 (33.7)	206 (26.6)	0.007	31.4%	31%	31.1%	0.99
Hypertension (n, %)	658 (75.1)	722 (77.4)	561 (72.6)	0.073	74.9%	75.6%	73.2%	0.72
CAD (n, %)	279 (31.8)	305 (32.7)	285 (36.9)	0.073	34.2%	33.1%	35.9%	0.69
AF (n, %)	265 (30.3)	324 (34.7)	192 (24.8)	<0.001	31.1%	29.4%	32.1%	0.70
Charlson index (%)	4.7 ± 2.3	4.8 ± 2.2	4.7 ± 2.2	0.46	4.9 ± 2.3	4.7 ± 2.2	4.8 ± 2.3	0.25
GFR (mL/s)	67 ± 31	66 ± 28	67 ± 29	0.39	67 ± 32	66 ± 28	67 ± 29	0.78
Echocardiographic data								
AVA (cm^2)	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001
AVAi (cm^2/m^2)	0.70 ± 0.07	0.48 ± 0.08	0.39 ± 0.09	<0.001	0.69 ± 0.07	0.49 ± 0.08	0.39 ± 0.09	<0.001
MG (mmHg)	20 ± 8	27 ± 8	5 ± 13	<0.001	20 ± 8	28 ± 7	53 ± 13	<0.001
Vmax (cm/s)	2.9 ± 0.5	3.3 ± 0.5	4.6 ± 0.5	<0.001	2.9 ± 0.5	3.4 ± 0.5	4.6 ± 0.5	<0.001
Svi < 35 mL/m^2 (n, %)	161 (18.4)	442 (47.4)	189 (24.5)	<0.001	29.9%	30.7%	29.5%	0.93
sPAP (mmHg)	34 ± 11	35 ± 12	35 ± 11	0.28	35 ± 13	34 ± 12	35 ± 11	0.60
sPAP ≥ 45 mmHg (n,%)	73 (8.3)	117 (12.5)	98 (12.7)	0.005	10.9%	10.9%	11.3%	0.98
EF (%)	64 ± 7	63 ± 8	63 ± 7	0.001	64 ± 8	64 ± 7	63 ± 7	0.67
AR2 (n, %)	22 (2.5)	22 (2.4)	40 (5.2)	0.002	3.2%	3.4%	3.4%	0.98

AF = atrial fibrillation; AR2 =aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; DLG-SAS = discordant low-gradient severe aortic stenosis; EF = ejection fraction; GFR = glomerular filtration rate; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis; MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

The unoperated population consisted of 1812 patients distributed as follows: 759 (42%) with MAS, 674 (37%) with DLG-SAS, and 379 (21%) with HG-SAS (**Table 2**). Overall, these patients shared clinical and imaging characteristics similar to those of the overall population. Noteworthy, there were more women in the DLG-SAS group. As for the overall population, after IPW, no significant difference in baseline characteristics persisted (**Table 2, right column**).

Table 2: Baseline and Inverse Probability Weighting (IPW)-Weighted Characteristics of the Unoperated Population.

	Unoperated Population (n = 1,812 Patients)				IPW Population			
	MAS N = 759	DLG-SAS N = 674	HG-SAS N = 379	*P*-Value	MAS N = 759	DLG-SAS N = 674	HG-SAS N = 379	*P*-Value
Clinical data								
Male sex (n, %)	404 (53.2)	298 (44.2)	181 (47.8)	0.003	48.4%	47.2%	48.6%	0.94
Age (y)	76 ± 11	80 ± 10	80 ± 9	<0.001	78 ± 10	79 ± 10	79 ± 10	0.82
BMI (kg/m^2)	27 ± 5	28 ± 6	27 ± 5	0.002	28 ± 6	27 ± 5	27 ± 6	0.49
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.009	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.84
NYHA I/II (n, %)	690 (90.9)	527 (78.2)	275 (72.6)	<0.001	82.1%	82.2%	81.2%	0.96
Angina (n, %)	105 (13.8)	89 (13.2)	63 (16.6)	0.29	14.7%	12.4%	14.1%	0.65
Syncope (n, %)	47 (6.2)	43 (6.4)	43 (11.3)	0.003	5.6%	6.5%	11.9%	0.017
Diabetes (n, %)	233 (30.7)	235 (34.9)	95 (25.1)	0.004	32.2%	31.7%	31.6%	0.99
Hypertension (n, %)	567 (74.7)	527 (78.2)	278 (73.4)	0.15	75%	76.1%	72.6%	0.67
CAD (n, %)	218 (28.7)	193 (28.6)	107 (28.2)	0.99	30%	28.5%	26.8%	0.73
AF (n, %)	235 (31.0)	257 (38.1)	112 (29.6)	0.003	33.8%	33%	37.3%	0.58
Charlson score (%)	4.9 ± 2.3	5.1 ± 2.2	5.1 ± 2.1	0.11	5.1 ± 2.2	4.9 ± 2.2	5.0 ± 2.3	0.46
GFR (mL/s)	66 ± 32	63 ± 28	61 ± 26	0.018	63 ± 30	63 ± 27	64 ± 28	0.77
Echocardiographic data								
AVA (cm^2)	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001	1.3 ± 0.2	0.9 ± 0.2	0.7 ± 0.2	<0.001
AVAi (cm^2/m^2)	0.70 ± 0.07	0.48 ± 0.08	0.39 ± 0.09	<0.001	0.70 ± 0.07	0.5 ± 0.08	0.39 ± 0.09	<0.001
MG (mmHg)	20 ± 8	26 ± 8	53 ± 13	<0.001	19 ± 8	27 ± 7	53 ± 12	<0.001
Vmax (cm/s)	2.9 ± 0.5	3.3 ± 0.5	4.6 ± 0.5	<0.001	2.8 ± 0.5	3.3 ± 0.5	4.6 ± 0.5	<0.001
Svi < 35 mL/m^2 (n, %)	142 (18.7)	340 (50.4)	102 (26.9)	<0.001	30.8%	32.6%	31.2%	0.87
sPAP (mmHg)	34 ± 11	36 ± 13	36 ± 12	0.039	36 ± 13	35 ± 12	36 ± 11	0.77
sPAP ≥ 45 mmHg (n,%)	65 (8.6)	88 (13.1)	54 (14.2)	0.004	10.8%	11.3%	12.4%	0.86
EF (%)	64 ± 8	63 ± 8	62 ± 7	<0.001	64 ± 8	64 ± 7	63 ± 7	0.69
AR2 (n, %)	18 (2.4)	17 (2.5)	23 (6.1)	0.002	3.2%	3.3%	3.4%	0.98

AF = atrial fibrillation; AR2 =aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; DLG-SAS = discordant low-gradient severe aortic stenosis; EF = ejection fraction; GFR = glomerular filtration rate; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis; MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

PREDICTORS OF OUTCOME AND SURVIVAL IN THE THREE AORTIC STENOSIS GROUPS. For the overall population, a multivariate model was built with 9 covariates (age, sex, BSA, NYHA functional class, diabetes mellitus status, atrial fibrillation history, Charlson comorbidity index, systolic pulmonary artery pressure >45 mmHg, and indexed stroke volume (SVi), **Table 3**), while

for the unoperated population, 7 covariates (age, BSA, NYHA functional class, atrial fibrillation history, Charlson comorbidity index, systolic pulmonary artery pressure >45 mmHg, and SVi, **Table 4**) were considered according to the parameters of univariate analysis. The echocardiographic parameters used for stratification of our groups (ie, AVAi and MG) were added separately to the multivariate model, and were both independently associated with survival for both the overall population (HR = 0.33, [0.2-0.55] 95% CI, P-value <0.001 for AVAi; HR = 1.05, [1.03-1.08] 95%CI; P-value <0.001 for MG) and the unoperated population (HR = 0.2, [0.12-0.33] 95%CI; P-value <0.001 for AVAi; HR = 1.07, [1.05-1.10]; P-value <0.001 for MG). During a median follow-up of 37.6 (IQR: 17.02) months, there were 770 AVRs and 1003 deaths in the overall population.

Table 3: Univariate and Multivariate Analysis of 5-Year All-Cause Mortality in the Overall Population.

	Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	***P*-Value**	**HR [95% CI]**	***P*-Value**
Male sex	0.85 [0.74;0.97]	0.016	1.27 [1.08;1.49]	0.004
Age by 5 y	1.37 [1.32;1.43]	<0.001	1.26 [1.20;1.33]	<0.001
BMI	0.96 [0.94;0.97]	<0.001		
BSA	0.37 [0.28;0.51]	<0.001	0.50 [0.34;0.73]	<0.001
NYHA (I, II, III, IV)	1.46 [1.35;1.57]	<0.001	1.30 [1.20;1.40]	<0.001
Angina	0.91 [0.75;1.1]	0.34		
Syncope	1.19 [0.93;1.52]	0.17		
Diabetes	1.17 [1.02;1.36]	0.03	1.19 [1.02;1.39]	0.026
Hypertension	0.92 [0.79;1.08]	0.32		
CAD	0.99 [0.86;1.15]	0.89		
AF	1.80 [1.57;2.07]	<0.001	1.33 [1.15;1.53]	<0.001
Charlson index	1.20 [1.17;1.24]	<0.001	1.08 [1.04;1.12]	<0.001
GFR (Cockroft) by 5 mL/min	0.92 [0.90;0.93]	<0.001		
AVA	0.30 [0.24;0.38]	<0.001		
AVAi	0.14 [0.09;0.23]	<0.001		
MG by 5 mmHg	1.06 [1.04;1.09]	<0.001		
Vmax	1.28 [1.18;1.38]	<0.001		
sPAP ≥ 45 mmHg	1.82 [1.51;2.20]	<0.001	1.26 [1.03;1.53]	0.023
EF by 5%	0.91 [0.87;0.95]	<0.001		
Svi by 5 mL/m^2	0.92 [0.89;0.95]	<0.001	0.94 [0.91;0.98]	0.001
AR2	1.50 [1.04;2.16]	0.03		

AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; EF = ejection fraction; GFR = glomerular filtration rate; MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

Table 4 : Univariate and Multivariate Analysis of 5-Year All-Cause Mortality in the Unoperated Population.

	Univariate Analysis		Multivariate Analysis	
	HR [95% CI]	***P*-Value**	**HR [95% CI]**	***P*-Value**
Male sex	0.94 [0.82;1.08]	0.40		
Age by 5 y	1.27 [1.22;1.32]	<0.001	1.15 [1.10;1.21]	**<0.001**
BMI	0.96 [0.95;0.98]	<0.001		
BSA	0.50 [0.37;0.68]	<0.001	0.71 [0.51;0.99]	**0.042**
NYHA (I, II, III, IV)	1.48 [1.38;1.58]	<0.001	1.33 [1.23;1.43]	**<0.001**
Angina	0.93 [0.77;1.12]	0.44		
Syncope	1.11 [0.87;1.42]	0.40		
Diabetes	1.18 [1.02;1.36]	0.027		
Hypertension	0.92 [0.78;1.07]	0.27		
CAD	1.17 [1.01;1.36]	0.03		
AF	1.63 [1.42;1.87]	<0.001	1.28 [1.12;1.48]	**0.001**
Charlson index	1.17 [1.14;1.20]	<0.001	1.10 [1.06;1.14]	**<0.001**
GFR (cockroft) by 5 mL/min	0.94 [0.92;0.95]	<0.001		
AVA	0.26 [0.20;0.33]	<0.001		
AVAi	0.09 [0.05;0.13]	<0.001		
MG by 5 mmHg	1.10 [1.08;1.12]	<0.001		
Vmax	1.45 [1.34;1.56]	<0.001		
sPAP ≥ 45 mmHg	1.75 [1.46;2.11]	<0.001	1.23 [1.01;1.49]	**0.042**
EF by 5%	0.91 [0.87;0.96]	<0.001		
Svi by 5 mL/m^2	0.93 [0.9;0.96]	0.001	0.96 [0.92;0.99]	**0.011**
AR2	1.52 [1.05;2.18]	0.026		

AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; EF = ejection fraction; GFR = glomerular filtration rate; MG = mean gradient; sPAP = systolic pulmonary

artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

Unsurprisingly, the HG-SAS group had the highest surgery rate (51% vs 27.8% vs 13.4% for DLG-SAS and MAS, respectively; P < 0.001). Survival in the overall cohort at 1, 3, and 5 years was 87%, 67.2%, and 50.6%, respectively. Five-year survival differed markedly according to AS groups. IPW-adjusted survival was worst for HG-SAS, intermediate for DLG-SAS, and best for MAS (41.2% vs 47% vs 58.9%, respectively; P < 0.001, **Figure 2A**). In the unoperated population, the median follow-up was 27.6 (IQR: 40.6) months. As for the overall population, but even more pronounced, 5-year IPW-adjusted survival was worst for HG-SAS, intermediate for DLG-SAS, and best for MAS (28.1% vs 37.9% vs 54.1%, respectively; P < 0.001, **Figure 2B**). When considering MAS as the reference group, the increased relative risk for mortality was 29% in the DLG-SAS group and 58% in the HG-SAS group for the entire patient cohort. A similar finding was observed in the unoperated population (40% relative risk in the DLG-SAS group and 88% relative risk in the HG-SAS group). When stratified according to SVi (<35 mL/m² vs >35 mL/m²), no difference in survival could be demonstrated into the DLG-SAS group (P = 0.16).

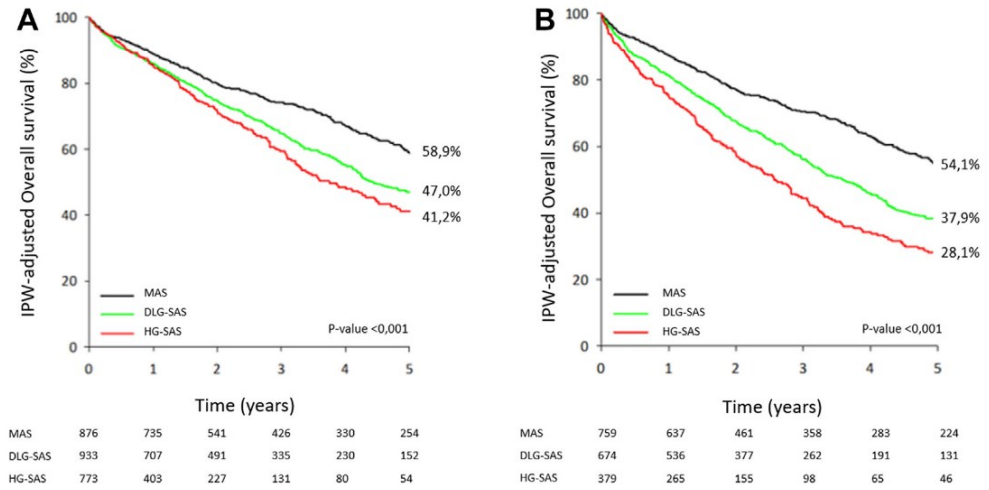


Figure 2: Five-Year Inverse Probability Weighting-Adjusted Overall Survival Curves. These curves compare survival among patients with MAS (black line), DLG-SAS (green line), and HG-SAS (red line) in the overall population (A) and in the unoperated population (B). Numbers at bottom indicate patients at risk. DLG-SAS = discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis; IPW = inverse probability weighting; MAS = moderate aortic stenosis.

PROGNOSTIC IMPACT OF MEAN GRADIENT. All patients with an AVAi <0.6 cm^2/m^2 (DLG-SAS vs HG-SAS patients) were selected and matched according to relevant clinical baseline characteristics, except for the transvalvular gradient (**Supplemental Table 1**). The analysis was carried out in the overall population (377 pairs) and in the unoperated population (193 pairs). The 5-year overall survival analysis using the Kaplan-Meier method on pairs of matched patients showed a better survival for DLG-SAS patients compared to HG-SAS patients (**Figure 3**), both in the overall population (45% vs 33%, respectively; P-value <0.001, **Figure 3A**) and in the unoperated population (36% vs 27%, respectively; P-value <0.002, **Figure 3B**). Taken together, these data demonstrate that for a comparable AVAi, the higher the MG, the worse the prognosis.

Supplemental Table 1: Characteristics of DLG-SAS and HG-SAS after PSM.

	Matched overall population			Matched unoperated population		
	DLG-SAS N=377	HG-SAS N=377	P-value	DLG-SAS N=193	HG-SAS N=193	P-value
Male sex (n, %)	203. (54)	187. (50)	0.27	95 (49)	96 (50)	>0.99
Age (years)	77 ± 11	78 ± 10	0.12	80 ± 9	81 ± 9	0.58
BMI (kg/m^2)	27.6 ± 5	27.7 ± 5	0.88	27.2 ± 5	27 ± 5	0.66
BSA (m^2)	1.88 ± 0.23	1.86 ± 0.22	0.23	1.86 ± 0.23	1.85 ± 0.21	0.60
NYHA I/II (n, %)	287 (76)	277 (74)	0.45	147 (76)	137 (71)	0.30
Angina (n, %)	57 (15)	64 (17)	0.55	24 (12)	32 (17)	0.31
Syncope (n, %)	25 (7)	30 (8)	0.58	10 (5)	28 (14)	0.004
Diabetes (n, %)	114 (30)	111 (29)	0.87	58 (30)	56 (29)	0.91
Hypertension (n, %)	288 (76)	291 (77)	0.86	144 (75)	145 (75)	>0.99
CAD (n, %)	133 (35)	121 (32)	0.40	53 (28)	56 (29)	0.82
AF (n, %)	100 (27)	107 (28)	0.62	67 (35)	64 (33)	0.83
Charlson score (%)	4.71 (2.21)	4.81 (2.06)	0.50	5.04 (1.94)	5.15 (1.95)	0.58
GFR (ml/s)	65 ± 27	66 ± 29	0.55	59 ± 23	62 ± 25	0.27
AVA (cm^2)	0.82 ± 0.18	0.80 ± 0.18	0.11	0.80 ± 0.19	0.78 ± 0.19	0.36
AVAi (cm^2/m^2)	0.44 ± 0.08	0.43 ± 0.09	0.29	0.43 ± 0.09	0.42 ± 0.09	0.45
MG (mmHg)	30. 6 ± 6.2	49.6 ± 9.8	**<0.001**	29.7 ± 7.0	49 ± 9.43	**<0.001**
Vmax (cm/s)	3.58 ± 0.40	4.43 ± 0.44	**<0.001**	3.52 ± 0.45	4.41 ± 0.44	**<0.001**
Svi<35ml/m^2 (n, %)	112 (29.7)	124 (32.9)	0.39	59 (31)	66 (34)	0.51
PAPs (mmHg)	34.6 ± 11.4	35.6 ± 11.4	0.34	36.6 ± 11.5	37.2 ± 12.2	0.66
PAPs>45mmHg (n, %)	47 (12)	55 (15)	0.46	27 (14)	31 (16)	0.67
EF (%)	63.2 ± 7.2	62.8 ± 7.3	0.51	62.7 ± 7.4	62.4 ± 7.7	0.73
AR2 (n, %)	14 (4)	17 (4.5)	0.71	10 (5.2)	9 (4.7)	>0.99

AF = atrial fibrillation; AR2 =aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; DLG-SAS = discordant low-gradient severe aortic stenosis; EF = ejection fraction; GFR = glomerular filtration rate; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis; MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

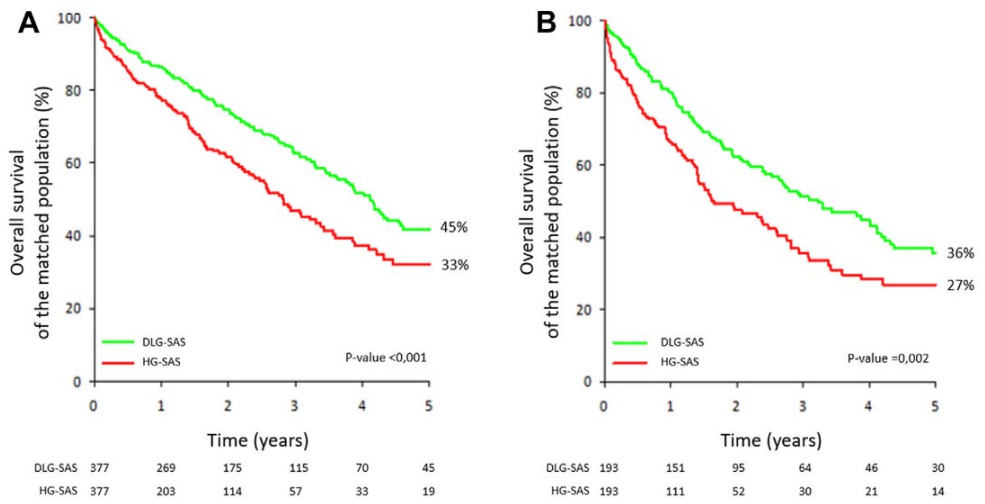


Figure 3: Five-Year Overall Survival Analysis Comparing Pairs of Matched Patients With an AVAi <0.6 cm²/m². These curves show a better survival for patients with DLG-SAS (green line) compared to those with HG-SAS (red line) in the overall population (A) as well as in the unoperated population (B). Numbers at bottom indicate patients at risk. AVAi = indexed aortic valve area; DLG-SAS = discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis.

PROGNOSTIC IMPACT OF AORTIC VALVE AREA. All patients with a MG ≤40 mmHg (MAS vs DLG-SAS patients) were selected and matched according to relevant clinical baseline characteristics, except for the AVA (**Supplemental Table 2).** The analysis was carried out in the overall population (448 pairs) and in the unoperated population (356 pairs). The 5-year overall survival analysis using the Kaplan-Meier method on pairs of matched patients showed a better survival for MAS patients compared to DLG-SAS patients (**Figure 4**), both in the overall population (52% vs 40%, respectively; P-value <0.001, **Figure 4A**) and in the unoperated population (46% vs 37%, respectively; P-value <0.001, **Figure 4B**). Taken together, these data demonstrate that for a comparable MG, the smaller the calculated AVAi, the worse the prognosis.

Supplemental Table 2: Characteristics of MAS and DLG-SAS after PSM.

	Matched overall population			Matched unoperated population		
	MAS N=448	DLG-SAS N=448	P-value	MAS N=356	DLG-SAS N=356	P-value
Male sex (n, %)	232 (51.8)	214 (47.8)	0.26	171 (48.0)	173 (48.6)	0.94
Age (years)	76.80 (10.67)	77.89	0.13	78.93 (10.03)	78.70 (9.82)	0.75
BMI (kg/m²)	27.95 (5.50)	27.28	0.064	27.87 (5.74)	27.23 (5.39)	0.12
BSA (m²)	1.87 (0.22)	1.86 (0.23)	0.26	1.86 (0.23)	1.85 (0.23)	0.53
NYHA I/II (n, %)	386 (86.2)	379 (84.6)	0.57	310 (87.1)	304 (85.4)	0.59
Angina (n, %)	62 (13.8)	55 (12.3)	0.55	51 (14.3)	44 (12.4)	0.51
Syncope (n, %)	27 (6.0)	27 (6.0)	>0.99	21 (5.9)	24 (6.7)	0.76
Diabetes (n, %)	145 (32.4)	159 (35.5)	0.36	113 (31.7)	125 (35.1)	0.38
Hypertension (n, %)	337 (75.2)	336 (75.0)	>0.99	266 (74.7)	268 (75.3)	0.93
CAD (n, %)	151 (33.7)	137 (30.6)	0.35	103 (28.9)	100 (28.1)	0.87
AF (n, %)	147 (32.8)	160 (35.7)	0.40	124 (34.8)	129 (36.2)	0.75
Charlson score (%)	5.03 (2.22)	4.83 (2.21)	0.17	5.20 (2.19)	4.99 (2.18)	0.20
GFR (ml/s)	67.15 (31.90)	63.45	0.075	63.81 (31.37)	61.56 (26.42)	0.32
AVA (cm²)	1.27 (0.18)	0.95 (0.17)	**<0.001**	1.27 (0.19)	0.95 (0.17)	**<0.001**
AVAi (cm²/m²)	0.68 (0.06)	0.51 (0.07)	**<0.001**	0.68 (0.06)	0.51 (0.07)	**<0.001**
MG (mmHg)	23.80 (9.39)	23.92	0.83	22.81 (9.24)	23.30 (7.43)	0.44
Vmax (cm/s)	3.10 (0.58)	3.16 (0.49)	0.096	3.04 (0.58)	3.12 (0.51)	0.086
Svi<35ml/m² (n, %)	140 (31.2)	135 (30.1)	0.77	121 (34.0)	114 (32.0)	0.63
PAPs (mmHg)	34.40 (11.33)	35.54	0.27	34.90 (12.21)	35.82 (13.08)	0.46
PAPs>45mmHg (n, %)	42 (9.4)	51 (11.4)	0.38	35 (9.8)	39 (11.0)	0.71
EF (%)	63.85 (7.51)	63.93	0.88	64.04 (7.42)	63.81 (7.85)	0.69
AR2 (n, %)	14 (3.1)	15 (3.3)	>0.99	9 (2.5)	11 (3.1)	0.82

AF = atrial fibrillation; AR2 =aortic regurgitation grade 2; AVA = aortic valve area; AVAi = indexed aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; DLG-SAS = discordant low-gradient severe aortic stenosis; EF = ejection fraction; GFR = glomerular filtration rate; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis; MG = mean gradient; sPAP = systolic pulmonary artery pressure; Svi = indexed stroke volume; Vmax = maximal transvalvular velocity.

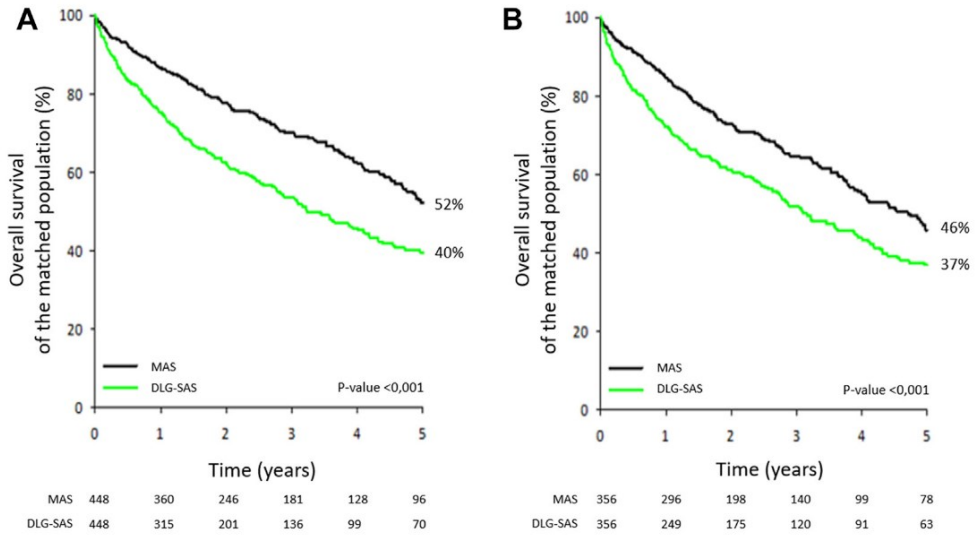


Figure 4: Five-Year Overall Survival Analysis Comparing Pairs of Matched Patients With a MG ≤40 mmHg. These curves show a better survival for patients with MAS (black line) compared to those with DLG-SAS (green line) in the overall population (A) as well as in the unoperated population (B). Numbers at bottom indicate patients at risk. DLG-SAS = discordant low-gradient severe aortic stenosis; MAS = moderate aortic stenosis.

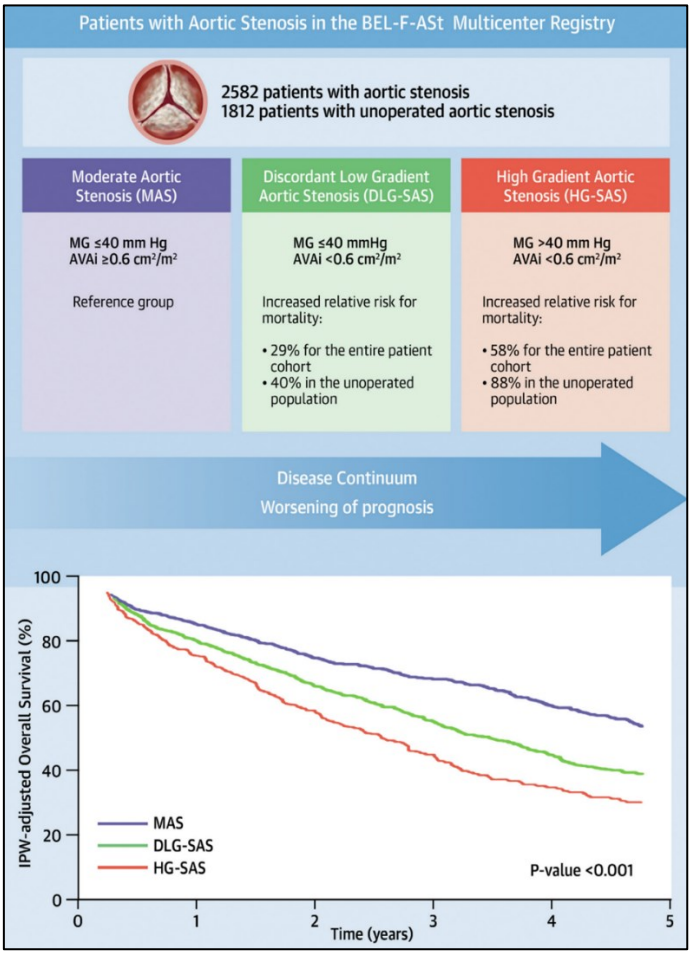
4. DISCUSSION

Our study evaluated the prognostic significance of DLG-SAS in a large, multicenter cohort of consecutive patients with AS. We compared the outcomes of this specific population with those of patients with MAS and HG-SAS. After a comprehensive adjustment for clinical variables, the prognosis of DLG-SAS patients was intermediate compared to that of MAS and HGSAS patients. At comparable MG, that is, when MAS patients were matched with DLG-SAS patients for the main clinical characteristics, the prognosis of patients was clearly dependent on valve area. The smaller the valve area, the worse the prognosis. Conversely, at comparable AVAi, that is, when DLG-SAS patients were matched with HG-SAS patients for the main

clinical characteristics, the prognosis of patients depended on pressure gradient. The higher the gradient, the worse the prognosis.

These findings remained consistent, regardless of whether a global population of AS patients (censored at the time of surgery) or a specific population of unoperated patients was considered.

One of the strengths of this work is the number of patients, allowing us to adjust for potentially important confounders, such as age, body mass index, NYHA status, CAD, Charlson score, atrial fibrillation, renal function, and ejection fraction. Indeed, unlike other studies that explored the prognosis of patients with AS, [95,158] our IPW analysis and propensity matching analysis allowed us to control for all the clinical differences between our 3 groups and to identify the prognostic implication exclusively related to echocardiographic parameters such as MG and AVAi. Furthermore, we did not consider the need for AVR as an endpoint of our study so as to focus exclusively on a hard endpoint, that is, overall mortality. We also decided to perform our analysis on 2 different populations. First, after exclusion of patients operated on within the first 3 months after the index echocardiography, we analyzed a global population of patients, some of whom had undergone surgery during their clinical follow-up. Second, we analyzed a population of patients who had not undergone surgery in their clinical course, to avoid the bias related to AVR. Based on our data, we can state that DLG-SAS is an intermediate form in the AS disease continuum, between MAS and HG-SAS (**Central Illustration**).



Central Illustration: The Disease Continuum of AS and the Prognostic Implications of the 3 Different Entities Classified According to MG and AVAi. When considering MAS as the reference group, the increased relative risk for mortality is 29% in the DLG-SAS group and 58% in the HG-SAS group for the entire patient cohort. A similar finding is observed in the unoperated population (40% relative risk in the DLG-SAS group and 88% relative risk in the HG-SAS group). DLG-SAS is an intermediate form in the disease continuum, HG-SAS being definitely the most malignant AS form. AVAi = indexed aortic valve area; DLG-SAS ¼ discordant low-gradient severe aortic stenosis; HG-SAS = high-gradient severe aortic stenosis; MAS = moderate aortic stenosis.

CONTROVERSY AROUND THE CLINICAL SIGNIFICANCE OF DISCORDANT LOW GRADIENT SEVERE AORTIC STENOSIS. There is an intense debate about the clinical significance and particularly about the real severity of DLGSAS. Some authors consider that DLG-SAS is a severe and advanced form of the disease that is associated with poor prognosis [97,99,158]. Others consider that it is a less severe form that can be safely monitored clinically [159,160,163]. Our study confirms that HG-SAS definitely has the worst prognosis when compared to MAS and DLG-SAS. A prospective study describing the natural history of MAS and DLG-SAS has shown that approximately 40% of patients progress to HG-SAS after a mean follow-up of 46 months [163]. This was subsequently confirmed by our research group [160]. These data provide a strong argument that DLG-SAS is a transient form of the disease evolving to a more severe form. Our data confirm this hypothesis from a strict prognostic perspective.

Low stroke volume has been proposed to be a major reason for a low transvalvular gradient in the presence of a normal ejection fraction and a potential cause for poorer prognosis [95]. Nevertheless, up to 50% of DLG-SAS patients have a normal stroke volume index, thereby highlighting that this parameter alone cannot explain the presence of low transvalvular gradient in case of an AVA <1cm^2 [132]. In our study, stroke volume was lower in the DLG-SAS group and low flow status was independently associated with overall mortality. Therefore, it was incorporated in the propensity score. After adjustment for this parameter, the prognosis of DLG-SAS remained significantly worse than that of MAS and better than that of HGSAS. Furthermore, as expected, patients with low flow DLG-SAS displayed a trend for a higher mortality risk compared with those with normal flow DLG-SAS, although not reaching the statistical significance (P = 0.063). However, after adjustment of covariates, we could not find any difference in mortality risk between the 2 DLG-AS entities (HR: 1.18, 95% CI: 0.93-1.48, P = 0.167). Our data are in line with the results of the prospective randomized SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study [163], while they are discordant with the retrospective analysis of Eleid et al [99]. There are 2

potential explanations for these discrepancies. First, in the study by Eleid et al, the groups were not matched for important clinical variables and second, unindexed AVA was used to define AS severity groups, which may have resulted in larger differences in body mass index between groups and thus have contributed to differences in outcomes.

DISCORDANT LOW GRADIENT SEVERE AORTIC STENOSIS: A LESS MALIGNANT FORM OF AORTIC STENOSIS. Several factors may explain why DLG-SAS is an intermediate form of AS. When clinicians use the continuity equation or the Gorlin formula for assessing AS severity, they measure the size of the functional orifice instead of that of the anatomical orifice [(27)]. In its simplified form, it neglects the coefficient of orifice contraction, a factor that compensates for the continuous convergence of fluid streamlines beyond a narrowed orifice. Under physiological flow conditions, the degree of underestimation of the anatomical orifice by the continuity equation is expected to be approximately 10% to 15%. Furthermore, standard calculation of AVA determined by continuity equation requires 3 measurements: AS jet velocity, LVOT diameter, and LVOT velocity. However, while LVOT was traditionally assumed to be circular, recent studies have shown that LVOT is often elliptical, thus leading to LV stroke volume underestimation by another 10% to 15% [(88,174)]. This has major consequences on AS classification, resulting in significant inconsistencies in AS severity assessment. Indeed, many patients thought to have SAS when assuming that the LVOT is circular turn out to have only MAS. Furthermore, when measuring the anatomical AVA instead of the functional AVA, larger AVAs are observed in patients with DLG-SAS compared to those with HG-SAS [(112)]. In addition, DLG-SAS patients exhibit less hypertrophy and fibrosis when compared to HGSAS patients [(194)]. Finally, It has been shown that DLG-SAS patients exhibit an aortic valve calcium load that is higher than that of MAS patients but lower than that of HG-SAS patients. Furthermore, although aortic valve calcium load was found to be predictive of DLG-SAS patient outcome, its prognostic impact is lower than in HG-SAS patients [(108)]. Taken

together, these data clearly challenge the view that DLG-SAS is a more advanced form of AS.

IMPLICATIONS AND PERSPECTIVES. Treating DLG-SAS or even MAS may likely improve the patient prognosis because of the progressive nature of the disease. However, the patients who will benefit the most from treatment are obviously those with HG-SAS. Our data demonstrate that patients with DLG-SAS have a better prognosis than those with HG-SAS. Transcatheter AVR is increasingly proposed and is becoming the reference treatment even in low-surgical-risk patients. Yet, this treatment is associated with significant risks and high costs [(222)]. Therefore, it is essential not to offer potentially futile treatment to patients who can be safely followed up clinically. This is especially true in case of frailty, advanced age, and multiple comorbidities. Our data support this view. These patients must be meticulously selected by weighing the treatment against the natural prognosis of the disease. Randomized prospective studies are needed to clarify the benefit of AVR for patients with DLG-SAS and help clinicians in making therapeutic decisions. Finally, considering our data and in accordance with international guidelines [(4,5)], the presence of a higher transvalvular gradient (ie, 30-40 mmHg vs 20-30 mmHg) and a smaller AVAi (ie, AVAi <0.45 cm^2/m^2 vs <0.6 cm^2/m^2) should guide clinicians in making treatment decisions in this particular DLG-SAS population.

LIMITATIONS. The study has several limitations that should be acknowledged. Because follow-up data were obtained retrospectively, this study presents the limitations inherent to this type of analysis. Our study exclusively concerned patients with preserved LVEF and without significant valve regurgitation and thus, the results cannot be extrapolated to patients with concomitant LV dysfunction or with complex multivalvular disease. Some variables previously reported as being risk factors for disease progression (ie, LV longitudinal strain, left atrial volume, B-type natriuretic peptide, and valve calcification) were not measured in this study, which limits the characterization of the different study groups. A substantial

number of patients were included in the 2000s. The recommendations at this time did not encourage routine calcium score in DLG-SAS patients.

5. CONCLUSION

In this large multicenter cohort, survival of DLG-SAS patients was better than that of HG-SAS patients and worse than that of MAS patients. Furthermore, at comparable MG, the smaller the calculated AVAi, the worse the prognosis, while at comparable AVAi, the higher the MG, the worse the prognosis. Taken together, these data argue that DLG-SAS is an intermediate form in the disease continuum, HG-SAS being definitely the most malignant AS form. Prospective studies are needed to clarify the benefit of AVR for DLG-SAS patients and help clinicians in making appropriate therapeutic decisions for this specific AS population.

6.2. STUDY 2: Quantifying the Survival Loss Linked to Late Therapeutic Indication in High-Gradient Severe Aortic Stenosis

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ABSTRACT

BACKGROUND. International guidelines recommend aortic valve replacement (AVR) as Class I triggers in high-gradient severe aortic stenosis (HGSAS) patients with symptoms and/or left ventricular ejection fraction (LVEF) <50%. The association between waiting for these triggers and postoperative survival penalty is poorly studied.

OBJECTIVES. The purpose of this study was to examine the impact of guideline-based Class I triggers on long-term postoperative survival in HGSAS patients.

METHODS. 2030 patients operated for HGSAS were included and classified as follows: no Class I triggers (no symptoms and LVEF >50%, n = 853), symptoms with LVEF >50% (n = 965), or LVEF <50% regardless of symptoms (n = 212). Survival was compared after matching (inverse probability weighting) for clinical differences. Restricted mean survival time was analyzed to quantify lifetime loss.

RESULTS. Ten-year survival was better without any Class I trigger than with symptoms or LVEF <50% (67.1% ± 3% vs 56.4% ± 3% vs 53.1% ± 7%, respectively, P < 0.001). Adjusted death risks increased significantly in operated patients with symptoms (HR: 1.45 [95% CI: 1.15-1.82]) or LVEF <50% (HR: 1.47 [95% CI: 1.05-2.06]) than in those without Class I triggers. Performing AVR with LVEF >60% produced similar outcomes to that of the general population, whereas operated patients with LVEF <60% was associated with a 10-year postoperative survival penalty. Furthermore, according to restricted mean survival time analyses, operating on symptomatic patients or with LVEF <60% led to 8.3- and 11.4-month survival losses, respectively, after 10 years, compared with operated asymptomatic patients with a LVEF >60%.

CONCLUSIONS. Guideline-based Class I triggers for AVR in HGSAS have profound consequences on long-term postoperative survival, suggesting that HGSAS patients should undergo AVR before trigger onset. Operating on patients with LVEF <60% is already associated with a 10-year postoperative survival penalty questioning the need for an EF threshold recommending AVR in HGSAS patients.

1. INTRODUCTION

Aortic valve stenosis (AS) affects 5% of adults >65 years old and is associated with a high mortality burden if not timely treated [(1)]. Due to the aging population and inherent progressive disease pattern, an increasing number of patients require aortic valve replacement (AVR) [(223)]. Indeed, without effective pharmaceutical treatment, AVR is the only intervention that can alter the patient's prognosis [(224)]. Severe AS (SAS) in its typical form, that is, high gradient severe AS (HGSAS), is defined as an aortic valve area (AVA) <1cm² or an indexed AVA <0.6 cm²/m² and a mean transvalvular gradient >40 mmHg or a peak jet velocity > 4m/s. Currently, the American Heart Association/American College of Cardiology and European Society of Cardiology/ European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines recommend AVR as Class I trigger for HGSAS if symptoms or a left ventricular ejection fraction (LVEF) <50% are present [(4,5)]. However, defining symptom presence can be challenging in patients who are sedentary, deconditioned, elderly, or in denial [(210)]. As a result, ESC/EACTS guidelines strongly recommend exercise testing to reveal hidden symptoms in asymptomatic SAS patients. Nevertheless, performing exercise tests in asymptomatic patients is rarely practiced (in <10% of eligible patients) [(34)]. LV function warrants valve replacement when impaired in SAS. However, LVEF becomes impaired late in the disease course. Furthermore, long-term survival of patients with LVEF <50% and SAS is poor despite AVR and regardless of symptoms [(9,213)]. In addition, recent magnetic resonance imaging-based studies have demonstrated that left ventricle structural and functional abnormalities may be common despite an LVEF >50% [(115,116)]. This could explain the reduced post operative survival of patients with an LVEF of 50 to 60% compared with those with an LVEF >60% [(9,156,213,225)]. As a result, the ESC/EACTS guidelines recommend AVR in asymptomatic patients with LVEF <55% as a Class IIa indication [(5)]. Yet, the optimal intervention timing in asymptomatic HGSAS patients and preserved LVEF is under debate. Since AVR ideally aims to restore patient life expectancy to that of the same age healthy population, a watchful waiting strategy raises the question of the

intrinsic risks of referring patients too late, with potential consequences regarding late postoperative survival. In this work, we sought to explore the impact of guideline-based Class I triggers on late postoperative survival rates in HGSAS patients. Therefore, we analyzed patients from the BEL-F-ASt (Belgian-French-Aortic Stenosis) registry, a multicenter international outcome registry pertaining to AS in routine practice. We investigated whether waiting for Class I triggers occurrence before operating on HGSAS patients would be associated with a late postoperative survival penalty.

2. METHODS

STUDY POPULATION AND DESIGN. Patients aged >18 years old diagnosed with at least mild AS in the echocardiography laboratories of 2 French (Amiens and Lille) and 1 Belgian (Brussels) tertiary hospitals between 2000 and 2020 were prospectively enrolled in the BEL-F-ASt registry (**Figure 1**). Enrolled patients underwent AVR within 3 months of the index echocardiography. AVR was surgical in 87.9% of patients and percutaneous in 12.1%. Coronary artery disease (CAD) was defined as the presence of a documented acute coronary syndrome history and previously confirmed by coronary angiography or coronary revascularization history. Symptoms were validated by each patient's personal cardiologist. Patients were retrospectively classified into 3 groups: no Class I trigger: asymptomatic with LVEF ≥50% (n = 853); symptomatic: dyspnea or/and angina or/ and syncope with LVEF ≥50% (n = 965); and LV dysfunction presence: LVEF <50% regardless of symptoms (n = 212). The study was conducted in agreement with the institutional policies and the revised Helsinki Declaration.

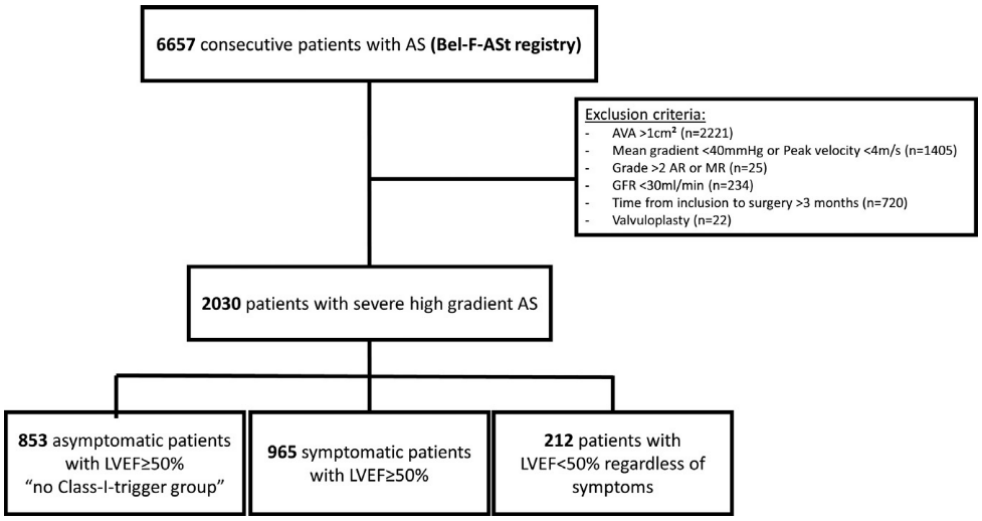


Figure 1: Flow Chart Illustrating Case Selection and Classification. AR = aortic valve regurgitation; AS = aortic valve stenosis; AVA = aortic valve area; GFR = glomerular filtration rate; LVEF = left ventricle ejection fraction; MR = mitral regurgitation.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive ultrasound examination including 2-dimensional echocardiography and Doppler examinations. Multiple transducer positions were systematically used to record maximal instantaneous and mean pressure gradients across the aortic valve. AVA was calculated by the continuity equation. In patients with atrial fibrillation (AF), 5 consecutive beats were systematically averaged. LV volumes and LVEF were calculated by using the biplane Simpson method.

FOLLOW-UP AND OUTCOMES. Selected patients underwent AVR within 3 months of the index assessment. AVR indication was decided by the cardiology team and the patient's physician. Clinical follow-up data were obtained by patient interview and telephone calls to physicians, patients, or their relatives if necessary. The surgery day was the first follow-up day and patients were censored at the time of last medical contact. The primary end point was overall postoperative mortality at 10 years.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD or median (IQR), depending on distribution normality, and categorical data as numbers (percentages). Baseline continuous data differences among the groups were explored using 1way analysis of variance (normally distributed data) or Kruskal-Wallis test (nonnormally distributed data). Pearson's chi-square test was used for categorical variables. Outcomes (all-cause mortality at 10 years) were displayed using the Kaplan-Meier method and compared between the 3 groups (no Class I trigger vs symptoms + LVEF >50% vs LVEF <50%) using 2-sided log-rank test. The observed survival of the no Class I trigger subgroup was compared using log-rank test with the expected survival of the general population which was similar in age and sex and provided by the World Health Organization database. A Cox proportional hazard survival model was built to determine the independent outcome-associated factors. For this purpose, a preliminary model was built from which Class I triggers (ie, symptoms and LVEF < 50%) were excluded. The ability of these class I triggers to improve the prediction of death by this preliminary model was tested and 4 different models were created. The proportional hazards assumption was confirmed using statistics and graphs based on Schoenfeld residuals. The model fit was evaluated with martingale and Cox-Snell residuals. The relationship between LVEF and the 10-year postoperative mortality risk was analyzed using a penalized smoothing spline. Hazard ratio (HR) values were calculated for each LVEF cutoff using a multivariate Cox regression. The maximum of the log-rank statistics was then calculated for LVEF thresholds (<50%, <55%, and <60%). An inverse probability weighting (IPW) analysis was performed to balance the baseline characteristics among groups with weighting to compare outcomes and further explore the prognostic value of the LVEF threshold. The inverse propensity score was calculated using the variables identified as independent mortality predictors in the multivariate analysis and additional echocardiographic confounders. These variables were used to estimate case weights using a multinomial logistic regression model to predict the inverse probability of having symptoms or LV dysfunction. Cox proportional hazard

regression models were adjusted for IPW to clarify the impact of symptoms and LV dysfunction on survival. Finally, the survival penalty was quantified according to AVR indication using restricted mean survival time (RMST) analysis at the truncated time point of 10 years. This method compares the mean survival time of each group in a pairwise analysis by subtracting the area under the survival curve to a specific time point. This analysis does not require a proportional hazard assumption, taking into account censored observations. RMST analysis was performed by integrating an adjusted Kaplan-Meier estimator with IPW. Statistical analyses were conducted using RStudio 1.4.1106. A P value of <0.05 was considered statistically significant.

3. RESULTS

BASELINE CHARACTERISTICS. The population comprised 2030 patients among which 853 (42%) underwent AVR without meeting a class I trigger, 965 (47.5%) while presenting symptoms and having an LVEF ≥50%, and 212 (10.5%) with an LVEF <50%, regardless of symptoms. Their demographic, clinical, and echocardiographic characteristics are summarized in **Table 1**. Patients who underwent AVR without meeting a class I trigger were younger and had a lower CAD and AF prevalence compared with those with symptoms or LV dysfunction. They also had better renal function and less comorbidities as well. Patients with LVEF <50% presented fewer symptoms compared with those included based on their symptomatic status. As anticipated, they had lower AVAs, transaortic peak velocities and lower stroke volumes, and higher systolic pulmonary pressures. There was no difference in CAD or AF prevalence between symptomatic patients with LVEF ≥50% and those with LVEF <50%. Notably, the operated patient proportion varied over time, whether they met a Class I trigger or not.

Table 1: Clinical and Echocardiographic Characteristics of Patients with Severe Aortic Stenosis According to the Trigger Group.

	All (N = 2,030)	(1) No Class I Trigger (n = 853, 42%)	(2) Symptoms and LVEF >50% (n = 965, 47.5%)	(3) LVEF <50% (n = 212, 10.5%)	*P* Value			
					Overall	(1) vs (2)	(1) vs (3)	(2) vs (3)
Clinical characteristics								
Age, y	76 ± 9	75 ± 10	76 ± 9	77 ± 8	<0.001	0.002	0.001	0.240
Male	53%	54%	49%	64%	<0.001	0.022	0.019	<0.001
BSA	1.88 ± 0.21	1.88 ± 0.21	1.88 ± 0.21	1.89 ± 0.21	0.652	0.989	0.633	0.682
NYHA functional class >II	34%	0%	60%	52%	<0.001	<0.001	<0.001	0.005
Angina pectoris	25%	0%	48%	23%	<0.001	<0.001	<0.001	<0.001
Syncope	11%	0%	21%	8%	<0.001	<0.001	<0.001	<0.001
Diabetes	25%	24%	27%	21%	0.161	0.323	0.323	0.274
Hypertension	70%	68%	73%	65%	0.008	0.024	0.450	0.024
CAD	52%	45%	57%	52%	<0.001	<0.001	0.113	0.215
AF	19%	17%	20%	26%	0.014	0.163	0.015	0.093
GFR (mL/m^2)	63 (48-81)	66 (50-85)	62 (48-79)	57 (46-76)	<0.001	0.018	<0.001	0.018
Charlson index	4 (3-6)	4 (3-5)	4 (3-5)	5 (3-6)	<0.001	0.040	<0.001	<0.001
EuroSCORE II	1.91 (1.26-3.06)	1.65 (1.03-2.43)	1.99 (1.33-3.25)	3.09 (2.16-5.08)	<0.001	<0.001	<0.001	<0.001
Echocardiographic parameters								
AVA, cm^2	0.66 ± 0.16	0.67 ± 0.16	0.66 ± 0.16	0.59 ± 0.15	<0.001	0.482	<0.001	<0.001
PG, mm Hg	90.6 ± 22.7	91.0 ± 22.1	91.1 ± 23.4	86.2 ± 21.4	0.015	0.988	0.019	0.013
MG, mm Hg	57.2 ± 14.7	57.5 ± 14.5	57.3 ± 14.8	55.1 ± 14.3	0.084	0.933	0.073	0.113
LVEDD, mm	48 ± 7	47 ± 7	47 ± 7	53 ± 7	<0.001	0.983	<0.001	<0.001
LVESD, mm	30 ± 8	29 ± 7	29 ± 7	41 ± 9	<0.001	0.491	<0.001	<0.001
LVEF, %	63 ± 11	65 ± 8	65 ± 8	40 ± 7	<0.001	0.991	<0.001	<0.001
iSV, mL/m^2	40 ± 10	41 ± 10	41 ± 10	35 ± 8	<0.001	0.198	<0.001	<0.001
sPAP, mm Hg	33 ± 11	32 ± 11	33 ± 11	39 ± 13	<0.001	0.620	<0.001	<0.001
AR grade 2	5.3%	4.1%	5.3%	9.9%	0.003	0.283	0.004	0.026
MR grade 2	3.8%	2%	3.9%	10%	<0.001	0.023	<0.001	<0.001
TR grade >1	3%	2.6%	2.8%	6.1%	0.022	0.887	0.040	0.040

Values are mean ± SD, %, or median (IQR). The comparison test for LVEF is shown for illustrative purposes because LVEF is part of the independent variable. AF = atrial fibrillation; AR = aortic regurgitation; AVA = aortic valve area; BSA = body surface area; CAD = coronary artery disease; GFR = glomerular filtration rate; iSV = indexed stroke volume; LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricle end-systolic diameter; MG = transaortic mean pressure gradient; MR = mitral regurgitation; NYHA = New York Heart Association; PG = transaortic peak pressure gradient; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

During patient enrollment (2000-2020), the symptomatic operated patient percentage decreased, whereas the asymptomatic operated patient proportion increased, suggesting that interventions were initiated earlier over time. However, the proportion of operated patients with an LVEF <50%

remained stable over time (**Figure 2**). Indications for AVR in patients without Class I trigger are shown in **Supplemental Table 1**.

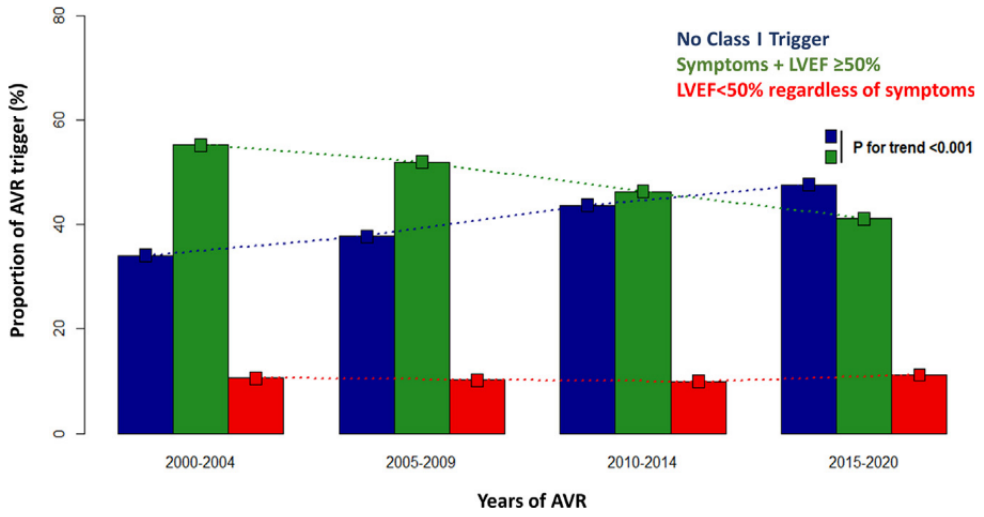


Figure 2: Temporal Evolution of the Operated HGSAS Patient Proportion Meeting a ClassI Trigger or Not. The symptomatic patient proportion who underwent surgery (green) significantly decreased over time, while patients with LVEF <50% (red) at the time of surgery remained stable. AVR = aortic valve replacement; HGSAS = high-gradient severe aortic stenosis; LVEF = left ventricle ejection fraction.

Supplemental Table 1: Indications for AVR in patients Without Class-I triggers.

Indications for AVR in patients without Class-I trigger (n=853)		**N**
Markedly elevated BNP (>300)	64 (21.1%)	303
Need for CABG	191 (22.4%)	853
Very Severe AS	329 (38.6%)	853
LVEF <55%	64 (7.5%)	853
Any of these reasons	510 (80.3%)	635

An indications was identified in 60% (510/853) of the patients in the no-Class-I trigger group.

POSTOPERATIVE SURVIVAL ACCORDING TO CLASS I TRIGGERS. During a median follow-up of 40 months (IQR: 17-74 months), 405 (20%) deaths were recorded, of which 52 (2.5%) occurred within the first 30 days after AVR. There was no difference in perioperative mortality among the groups (P = 0.37). Overall perioperative mortality decreased between the first and second recruitment decade (3.9% vs 1.7%, P = 0.005). The 10-year postoperative survival rate was better in patients without Class I trigger than in those with symptoms or LVEF <50% (67.1% ± 3% vs 56.4% ± 3% vs 53.1% ± 7%, respectively, P < 0.001). However, patients who underwent AVR without meeting Class I triggers did not achieve the anticipated survival rates compared with the age- and sex-matched general population (67.1% vs 72.0%, P = 0.03) (**Figure 3A**).

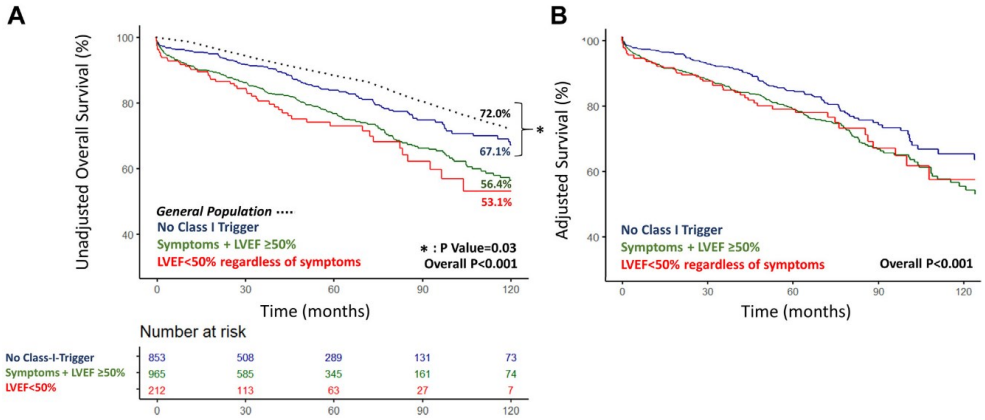


Figure 3: 10-Year Postoperative Survival Curves of High-Gradient Severe Aortic Stenosis Patients According to the Guideline Trigger Group. Graphs comparing unadjusted (A) and Cox-adjusted (B) survival among patients with no Class I trigger (blue line), symptoms (green line), and left ventricular ejection fraction <50% (red line). The doted black line represents the age- and sex- matched general population. The adjustments included age,

diabetes, coronary artery disease, renal function, and aortic valve area. LVEF = left ventricle ejection fraction.

Then, a basal multivariate Cox model was built with 5 covariates (age, diabetes, CAD, renal function, and AVA). By adding the Class I triggers to this model, symptom presence and/or LV dysfunction remained associated with increased mortality (**Table 2**). Different models were built. In model 1, symptoms (HR: 1.46, 95% CI: 1.17-1.81, P < 0.001) and LVEF expressed as a continuous variable (HR: 0.95, 95% CI: 0.91-0.99), P = 0.019) added significant strength in predicting death risks. Furthermore, when presenting LVEF as a categorical variable and when considering patients without Class I trigger as the reference group (model 2) (**Table 2**), the mortality relative risk increased with an adjusted HR: 1.45 (95% CI: 1.15-1.82, P = 0.002) in the symptomatic group and with an adjusted HR: 1.47 (95% CI: 1.05-2.06, P = 0.024) in the LVEF <50% group (**Figure 3B**).

Table 2: Multivariate Cox Models

		Hazard Ratio [95% CI]	*P* Value
Basal model			
	Age (per 5 y)	1.24 (1.14-1.35)	<0.001
	Diabetes	1.43 (1.14-1.79)	0.002
	CAD	1.37 (1.11-1.70)	0.003
	GFR (per 5 mL)	0.95 (0.93-0.98)	0.002
	AVA	0.40 (0.21-0.77)	0.006
Additional prognostic variables to basal model			
Model 1	Symptoms	1.46 (1.17-1.81)	<0.001
	LVEF by 5%	0.95 (0.91-0.99)	0.019
Model 2	No Class I trigger	Ref	-
	Symptoms + LVEF >50%	1.45 (1.15-1.82)	0.002
	LVEF <50%	1.47 (1.05-2.06)	0.024
Model 3	No Symptoms + LVEF >55%	Ref	-
	Symptoms + LVEF >55%	1.50 (1.17-1.92)	0.001
	LVEF <55%	1.92 (1.44-2.55)	<0.001
Model 4	No Symptoms + LVEF >60%	Ref	-
	Symptoms + LVEF >60%	1.60 (1.21-2.11)	<0.001
	LVEF <60%	2.00 (1.52-2.65)	<0.001

AVA = aortic valve area; CAD = coronary artery disease; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction.

PROGNOSTIC IMPACT OF LVEF THRESHOLD. To explore the prognostic impact of LVEF thresholds, we built a multivariate Cox model using a 55% EF and a 60% EF cutoff (model 3 and model 4, respectively) (**Table 2**). With an LVEF <55% and when considering patients without Class I trigger as the reference group, the mortality relative risk increased with an adjusted HR: 1.50 (95% CI: 1.17-1.92, P = 0.001) in the symptomatic group with LVEF >55% and with an adjusted HR: 1.92 (95% CI: 1.44-2.55, P < 0.001) in the LVEF <55% group. Similarly, with an LVEF <60% and when considering patients without Class I trigger as the reference group, the mortality relative risk already increased with an adjusted HR: 1.60 (95% CI: 1.21-2.11, P < 0.001) in the symptomatic group with LVEF >60% and with an adjusted HR: 2.00 (95% CI: 1.52-2.65, P < 0.001) in the LVEF <60% group.

Therefore, we used these different LVEF thresholds (ie, <55% and <60%) to redefine our groups (**Supplemental Tables 2 and 3**).

Supplemental Table 2: Clinical and echocardiographic characteristic in patients with HGSAS according to the trigger-group and LV dysfunction defined as LVEF <55%.

	ALL	**No symptom nor LV-dysfunction defined as LVEF<55%**	**Symptoms and LVEF>55%**	**LV dysfunction defined as LVEF<55%**	***P*-overall**	**p.1 vs 2**	**p.1 vs 3**	**p.2 vs 3**
	N=2030	N=789 (39%)	N=871 (43%)	N=370 (18%)				
Clinical characteristics								
Age, y	76 ± 9	75 ± 10	76 ± 9	77 ± 8	<0,001	0.003	0.001	0.541
Male sex (%)	53%	54%	48%	61%	<0,001	0.025	0.025	<0,001
BSA	1.88±0.21	1.88±0.22	1.88±0.21	1.90±0.22	0.302	0.994	0.359	0.306
NYHA>2 (%)	34%	0%	59%	48%	<0,001	<0,001	<0,001	<0,001
Angina pectoris (%)	25%	0%	49%	24%	<0,001	<0,001	<0,001	<0,001
Syncope (%)	11%	0%	21%	9%	<0,001	<0,001	<0,001	<0,001
Diabetes (%)	25%	24%	25%	27%	0.602	0.871	0.677	0.677
Hypertension (%)	70%	68%	73%	66%	0.010	0.035	0.434	0.023
CAD (%)	52%	45%	58%	53%	<0,001	<0,001	0.020	0.124
AF (%)	19%	17%	19%	26%	0.001	0.326	0.001	0.007
GFR (mL/m²)	63 [48;81]	66 [50;84]	62 [48;79]	60 [47;79]	0,002	0.026	0,003	0.145
Charlson Index	4 [3;6]	4 [3;5]	4 [3;5]	4 [3;6]	<0,001	0.099	<0,001	<0,001
EuroSCORE II	1.91 [1.26;3.06]	1.63 [1.02;2.42]	1.99 [1.33;3.22]	2.62 [1.75;4.38]	<0,001	<0,001	<0,001	<0,001
Echocardiographic parameters								
AVA, cm²	0.66 ± 0.16	0.67 ± 0.16	0.67 ± 0.16	0.61 ± 0.16	<0,001	0.764	<0,001	<0,001
PG, mmHg	90.6 ± 22.7	91.0 ± 21.8	91.5 ± 23	87.3 ± 23.5	0.008	0.899	0.023	0.007
MG, mmHg	57.2 ± 14.7	57.6 ± 14.5	57.5 ± 14.8	55.3 ± 14.6	0.029	0.994	0.036	0.041
LVEDD, mm	48 ±7	47 ±7	47 ± 7	52 ±8	<0,001	0.872	<0,001	<0,001
LVESD, mm	30 ±8	29 ± 6	29 ± 7	38 ± 9	<0,001	0.919	<0,001	<0,001
LVEF, %	**63** ± 11	**66** ± 7	**67** ± 7	**45** ± 8	**<0.001**	**0.463**	**<0.001**	**<0.001**
Svi, ml/m²	40 ±10	41 ±10	41 ±10	36 ± 9	<0,001	0.482	<0,001	<0,001
sPAP, mmHg	33 ±11	32 ±10	32 ± 11	38 ± 14	<0,001	0.880	<0,001	<0,001
AR grade-2 (%)	5.3%	4.4%	5.2%	7.3%	0.125	0.562	0.181	0.272
MR grade-2 (%)	3.8%	2.2%	3.4%	8.1%	<0,001	0.152	<0,001	0,001
TR grade>1 (%)	3%	2.5%	2.6%	5.1%	0.036	1.000	0.060	0.060

AF = atrial fibrillation; AR = aortic regurgitation; AVA = aortic valve area; BSA = body surface area; CAD = coronary artery disease; GFR = glomerular filtration rate; iSV = indexed stroke volume; LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricle end-systolic diameter; MG = transaortic mean pressure gradient; MR = mitral regurgitation; NYHA = New York Heart Association; PG = transaortic peak pressure gradient; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

Supplemental Table 3: Clinical and echocardiographic characteristic in patients with HGSAS according to the trigger-group and LV dysfunction defined as LVEF <60%.

	ALL	No symptom nor LV-dysfunction defined as LVEF<60%	Symptoms and LVEF>60%	LV dysfunction defined as LVEF<60%	*P*-overall	p.1 vs 2	p.1 vs 3	p.2 vs 3
	N=2030	N=660 (33%)	N=714 (35%)	N=656 (32%)				
Clinical characteristics								
Age, y	76 ± 9	74 ± 10	76 ± 9	76 ± 9	<0,001	0.001	0.003	0.933
Male sex (%)	53%	53%	47%	59%	<0,001	0.025	0.025	<0,001
BSA	1.88±0.21	1.87±0.22	1.87±0.21	1.89±0.22	0.096	0.995	0.165	0.127
NYHA>2 (%)	34%	0%	60%	41%	<0,001	<0,001	<0,001	<0,001
Angina pectoris (%)	25%	0%	50%	24%	<0,001	<0,001	<0,001	<0,001
Syncope (%)	11%	0%	20%	11%	<0,001	<0,001	<0,001	<0,001
Diabetes (%)	25%	24%	25%	27%	0.480	0.620	0.620	0.620
Hypertension (%)	70%	68%	74%	67%	0.003	0.020	0.544	0.005
CAD (%)	52%	45%	57%	53%	<0,001	<0,001	0.007	0.082
AF (%)	19%	16%	18%	25%	0.001	0.281	<0.001	0.003
GFR (mL/m²)	63 [48;81]	66 [50;84]	62 [48;78]	62 [48;82]	0,030	0.040	0,055	0.794
Charlson Index	4 [3;6]	4 [3;5]	4 [3;5]	4 [3;6]	0,002	0.056	0,001	0.124
EuroSCORE II	1.91 [1.26;3.06]	1.60 [1.01;2.39]	2.03 [1.34;3.32]	2.18 [1.39;3.55]	<0,001	<0,001	<0,001	0.048
Echocardiographic parameters								
AVA, cm²	0.66 ± 0.16	0.68 ± 0.16	0.67 ± 0.16	0.63 ± 0.16	<0,001	0.627	<0,001	<0,001
PG, mmHg	90.6 ± 22.7	91.4 ± 22.2	91.5 ± 22.3	88.7 ± 23.5	0.036	1.00	0.069	0.061
MG, mmHg	57.2 ± 14.7	57.7 ± 14.6	57.4 ± 14.5	56.4 ± 15.0	0.242	0.931	0.246	0.412
LVEDD, mm	48 ±7	47 ±7	46 ± 7	50 ±8	<0,001	0.566	<0,001	<0,001
LVESD, mm	30 ±8	28 ± 6	28 ± 7	35 ± 8	<0,001	0.948	<0,001	<0,001
LVEF, %	63 ± 11	68 ± 6	69 ± 6	51 ± 8	<0.001	0.128	<0.001	<0.001
Svi, ml/m²	40 ±10	42 ±10	41 ±10	38 ± 9	<0,001	0.443	<0,001	<0,001
sPAP, mmHg	33 ±11	32 ±10	32 ± 10	35 ± 13	<0,001	0.774	<0,001	<0,001
AR grade-2 (%)	5.3%	4.4%	5.2%	6.25%	0.319	0.578	0.505	0.578
MR grade-2 (%)	3.8%	2.3%	2.7%	6.6%	<0,001	0.772	0,001	0,001
TR grade>1 (%)	3%	2.3%	2.7%	4.3%	0.082	0.772	0.180	0.207

AF = atrial fibrillation; AR = aortic regurgitation; AVA = aortic valve area; BSA = body surface area; CAD = coronary artery disease; GFR = glomerular filtration rate; iSV = indexed stroke volume; LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricle end-systolic diameter; MG = transaortic mean pressure gradient;

MR = mitral regurgitation; NYHA = New York Heart Association; PG = transaortic peak pressure gradient; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

As observed in patients with a LVEF <50%, asymptomatic patients without LV dysfunction had a better survival rate compared to symptomatic patients or those presenting with LV dysfunction, regardless of whether the LVEF threshold was set at LVEF <55% (68.6% ± 3% vs 57.4% ± 3% vs 50.9% ± 5%, respectively, P < 0.001), or LVEF <60% (72.3% ± 3% vs 56.7% ± 3% vs 52.2% ± 4%, respectively, P < 0.001) (**Figure 4**). Interestingly, performing AVR in asymptomatic patients with LVEF >55% yielded similar outcomes to those observed in the general population (**Figure 4A**). This was even more striking for asymptomatic patients operated on with an LVEF >60% (**Figure 4B**). After adjustment, 10-year survival curves showed a better survival in asymptomatic patients without LV dysfunction compared to those with symptoms or with depressed LVEF regardless of EF (**Figures 4C and 4D**).

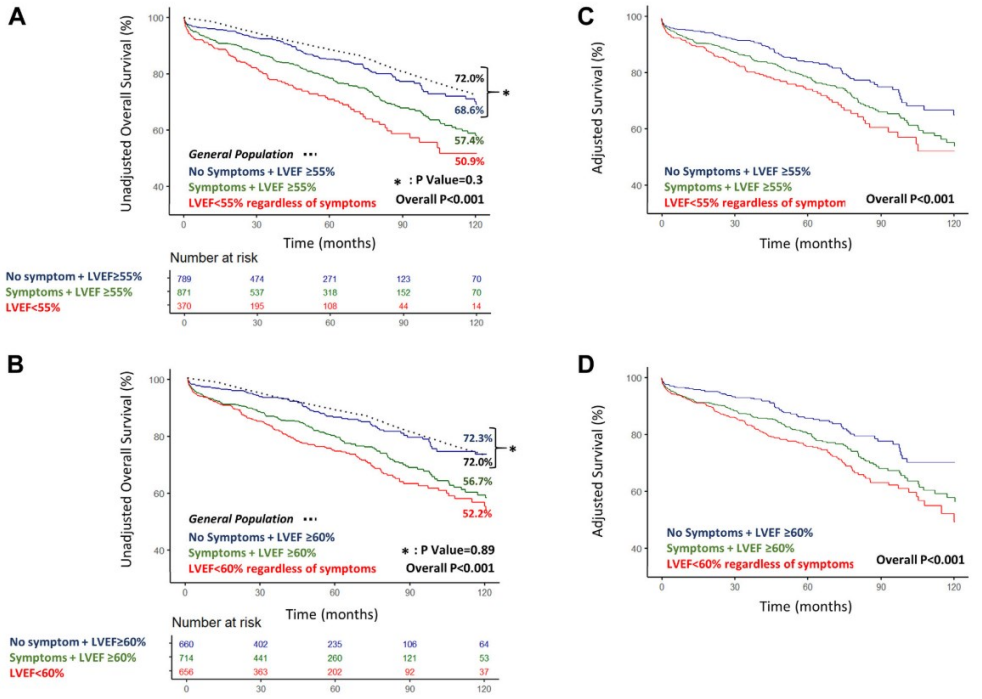


Figure 4: 10-Year Postoperative Survival Curves of High-Gradient Severe Aortic Stenosis Patients According to LVEF Thresholds and Symptoms. (A) Graph comparing unadjusted survival among asymptomatic patients with LVEF ≥55% (blue line), symptoms (green line), and LVEF <55% (red line). (B) Graph comparing unadjusted survival among asymptomatic patients with LVEF ≥60% (blue line), symptoms (green line), and LVEF <60% (red line). The doted black line represents the age- and sex-matched general population. (C) Graph comparing Cox-adjusted survival among asymptomatic patients with LVEF ≥55% (blue line), symptoms (green line), and LVEF <55% (red line). (D) Graph comparing Cox-adjusted survival among asymptomatic patients with LVEF ≥60% (blue line), symptoms (green line), and LVEF <60% (red line). The adjustments included age, diabetes, coronary artery disease, renal function, and aortic valve area. LVEF = left ventricular ejection fraction.

We also observed a survival penalty among asymptomatic patients who underwent surgery with a LVEF ranging from 55% to 60% (**Figure 5**), suggesting that it is primarily asymptomatic patients operated on with an LVEF >60% who achieved a prognosis comparable to the general population.

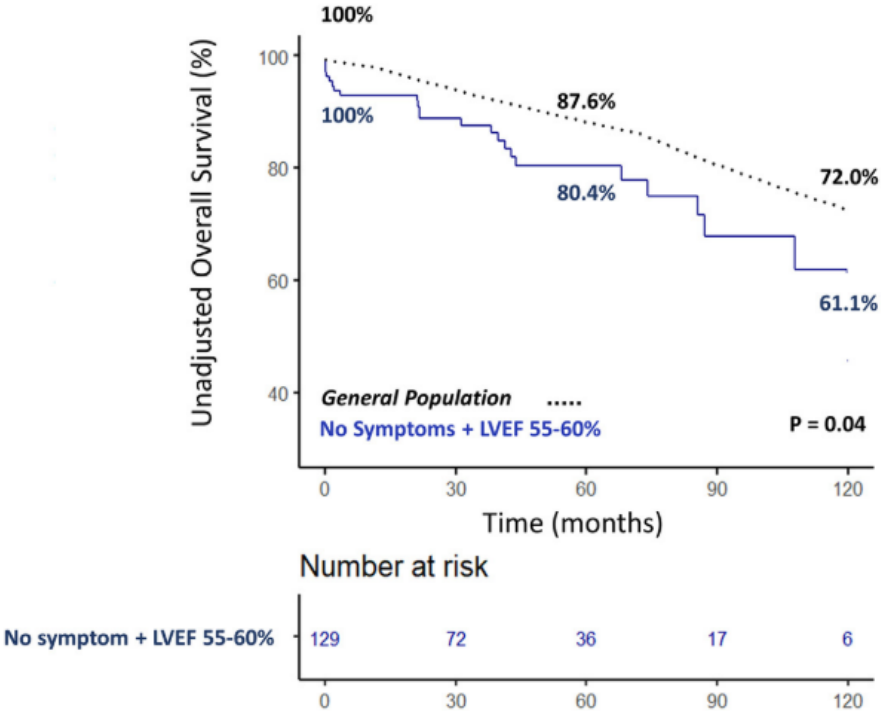


Figure 5: Unadjusted 10-Year Postoperative Survival Curves of Asymptomatic Patients with a LVEF Ranging From 55% to 60%. The doted black line represents the age- and sex-matched general population. LVEF = left ventricular ejection fraction.

The relationship between LVEF and the postoperative death risk was represented as a penalized smoothing spline function. After adjustment for confounding variables, there was an increased mortality risk with a decreasing LVEF significant below 60% (**Figure 6**).

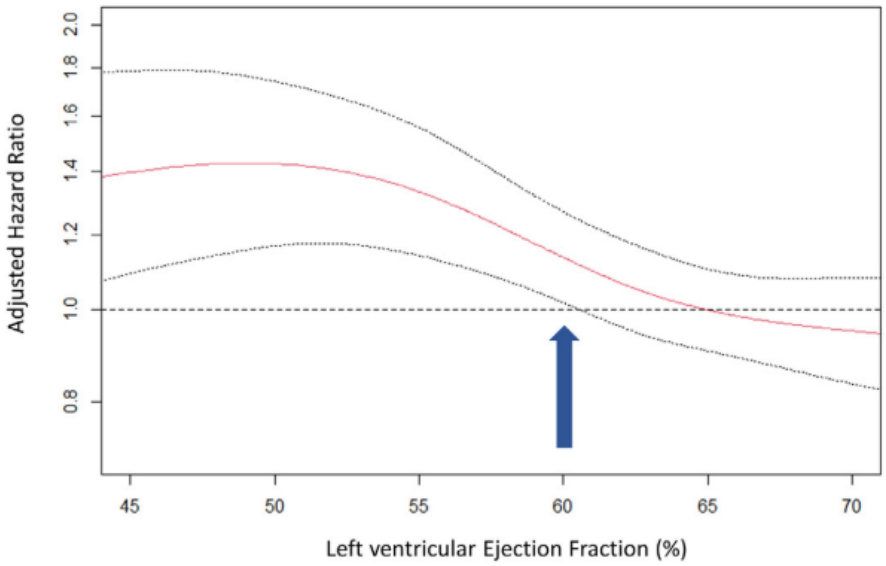


Figure 6: Postoperative Mortality Risk Estimated Using Spline Function for Left Ventricular Ejection Fraction. HR (solid red line) and 95% CI (dashed lines) were estimated using a Cox multivariate model, with left ventricular ejection fraction represented as a penalized spline function. There was an increased mortality risk with decreasing LVEF which becomes significant below 60% (arrow). The model was adjusted for age, diabetes, aortic valve area, coronary artery disease, renal function, and symptoms.

The risk increased with a higher slope in the LVEF range between 60 and 55% and then flattened out between 55 and 50%. When considering the lowest HR point in the spline shape as reference, all patients with LVEF <60%, LVEF <55%, or LVEF <50% had significantly worse prognosis (HR: 1.14, 95% CI: 1.021.27; HR: 1.33, 95% CI: 1.14-1.56 and HR: 1.43, 95% CI: 1.17-1.74, respectively), pointing out that patients with LVEF <60% were already at risk. Then, survival differences were analyzed using the maximum logrank statistics (**Figure 7**). Compared with LVEF <50% threshold (maximum log rank statistic: 2.8; P = 0.002) (**Figure 7A**), the maximum statistic was observed for a LVEF <55% threshold (log rank statistic: 4.2; P < 0.001) (**Figure 7B**) and for

a LVEF <60% threshold (log rank statistic: 4.2; P < 0.001) (**Figure 7C**) resulting in a greater separation of the survival curves.

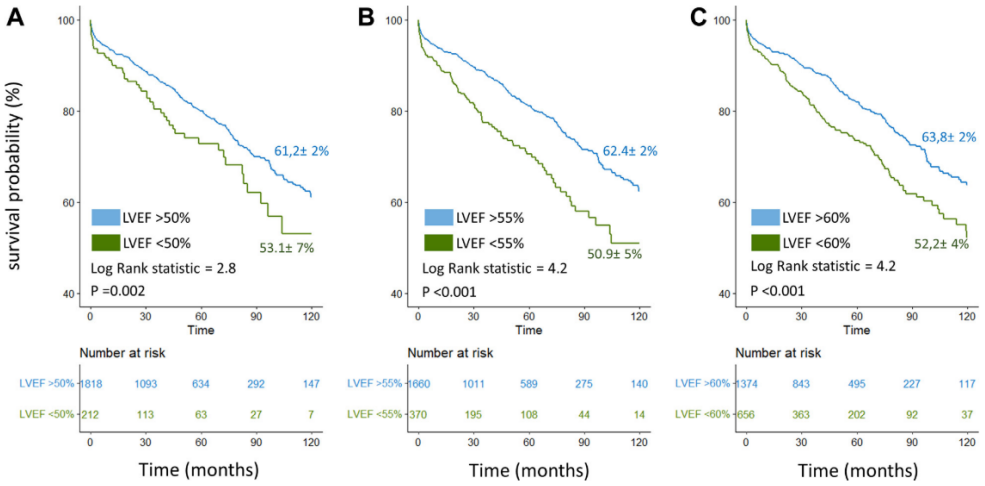


Figure 7: Ten-Year Survival Curves Based on LVEF Thresholds. Compared to the threshold of left ventricular ejection fraction (LVEF) <50% (A), the maximum Log Rank-statistic was observed for an LVEF <55% and LVEF <60% threshold resulting in a greater separation of the survival curves (B and C). Numbers indicate patients at risk.

Finally, IPW was used to comprehensively balance the baseline characteristics between groups and to compare survival. After IPW, no significant difference in baseline characteristics persisted (**Supplemental Tables 4A and 4B**). IPW showed that in comparison with patient without Class I trigger, symptoms at the time of AVR was associated with excess postoperative mortality (HR: 1.43; 95% CI: 1.13-1.82) and a LVEF <55% or a LVEF <60% at the time of AVR had an even higher excess risk (HR: 1.63; 95% CI: 1.19-2.23, and HR: 1.79; 95% CI: 1.36-2.36, respectively), similar to standard Cox-proportional hazard analysis.

Supplemental Table 4A: Post-IPW baseline characteristics in patients with HGSAS according to the trigger-group and LV dysfunction defined as LVEF <55%.

	No Class-I-trigger	Symptoms	LVEF<55%	P-value	SMD
Age, year	75.6±9.5	75.5±9.0	74.8±9.6	0.575	0.06
Male sex	52,5%	52.8%	50.4%	0.847	0.03
BMI, kg/m²	27.9±5.0	27.9±5.2	28.2±5.4	0.778	0.04
BSA, m²	1.9±0.2	1.9±0.2	1.9±0.2	0.556	0.06
Diabetes	25.1%	24.8%	27.6%	0.752	0.04
Hypertension	69.6%	69.5%	67.8%	0.905	0.03
Coronary disease	52.2%	51.6%	50.8%	0.951	0.02
Atrial fibrillation	19.3%	18.9%	22,7%	0.526	0.06
Cockroft, ml/min/1.73	68.9±26.5	68.0±26.5	67.1±23.5	0.746	0.05
Charlson index	4.3±1.8	4.2±1.9	4.4±2.0	0.529	0.06
AVA, cm²	0.66±0.16	0.66±0.16	0.66±0.16	0.976	0.01
AVAi,cm²/m²	0.35±0.09	0.35±0.08	0.35±0.08	0.750	0.04
Mean gradient, mmHg	57.1±14.4	57.3±14.7	57.3±15.3	0.952	0.01
Peak velocity, m/s	4.7±0.5	4.7±0.6	4.7±0.6	0.657	0.05
LVEDD, mm	46.7±7.0	46.8±6.9	51.8±7.9	<0,001	0.46
LVESD, mm	28.9±6.5	29.1±7.0	37.4±9.0	<0,001	0.70
LVEF, %	66.2±6.9	66.7±7.4	46.6±7.4	<0,001	1.85
SVi, ml/m²	40.1±10.3	40.2±9.9	39.5±9.9	0.752	0.04
sPAP >45mmHg	12.7%	12.0%	11.8%	0.958	0.02
Grade 2 AR	5.0%	5.3%	7.5%	0.450	0.07
Grade 2 MR	4.8%	4.0%	4.2%	0.848	0.03
Grade >1 TR	3.9%	2.6%	3.4%	0.560	0.05

AF = atrial fibrillation; AR = aortic regurgitation; AVA = aortic valve area; BSA = body surface area; CAD = coronary artery disease; GFR = glomerular filtration rate; iSV = indexed stroke volume; LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricle end-systolic diameter; MG = transaortic mean pressure gradient; MR = mitral regurgitation; NYHA = New York Heart Association; PG = transaortic peak pressure gradient; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

Supplemental Table 4B: Post-IPW baseline characteristics in patients with HGSAS according to the trigger-group and LV dysfunction defined as LVEF <60%.

	No Class-I-trigger	Symptoms	LVEF<60%	P-value	SMD
Age, year	75.6±9.4	75.5±9.0	75.5±9.3	0.992	0.01
Male sex	52,3%	52.9%	52.1%	0.972	0.01
BMI, kg/m²	27.9±5.0	27.9±5.2	28.1±5.4	0.824	0.03
BSA, m²	1.9±0.2	1.9±0.2	1.9±0.2	0.443	0.06
Diabetes	25.2%	24.8%	25.9%	0.947	0.02
Hypertension	69.9%	69.3%	69.7%	0.984	0.01
Coronary disease	52.2%	51.8%	51.4%	0.986	0.01
Atrial fibrillation	17.6%	17.9%	23.4%	0.103	0.09
Cockroft, ml/min/1.73	68.5±26.3	67.3±25.8	68.3±26.7	0.826	0.03
Charlson index	4.3±1.8	4.2±1.9	4.4±2.0	0.518	0.05
AVA, cm²	0.66±0.16	0.66±0.16	0.66±0.16	0.997	0.01
AVAi,cm²/m²	0.35±0.09	0.35±0.08	0.35±0.08	0.817	0.03
Mean gradient, mmHg	58±15	57±14	57±15	0.795	0.03
Peak velocity, m/s	4.7±0.6	4.7±0.6	4.7±0.6	0.286	0.07
LVEDD, mm	46.5±7.0	46.4±7	50.2±8	<0,001	0.35
LVESD, mm	28.2±6	28.2±7	35±8	<0,001	0.61
LVEF, %	68±6	69±6	51±8	<0,001	1.63
SVi, ml/m²	40±10	40±10	40±9.6	0.667	0.04
sPAP >45mmHg	11.8%	12.2%	12.2%	0.982	0.01
Grade 2 AR	4.5%	5.6%	3.9%	0.671	0.05
Grade 2 MR	4.3%	4.1%	3.9%	0.957	0.03
Grade >1 TR	3.3%	2.7%	3.5%	0.795	0.06

AF = atrial fibrillation; AR = aortic regurgitation; AVA = aortic valve area; BSA = body surface area; CAD = coronary artery disease; GFR = glomerular filtration rate; iSV = indexed stroke volume; LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricle end-systolic diameter; MG = transaortic mean pressure gradient; MR = mitral regurgitation; NYHA = New York Heart Association; PG = transaortic peak pressure gradient; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

RMST ANALYSIS. The RMST analysis was performed on the IPW-adjusted population. A mean survival penalty was estimated at 10 years following AVR by comparing groups based on their guideline triggers. After 10 years, when compared with patients operated on without any triggers (no symptoms or

LV dysfunction defined by a LVEF < 60%), operating on patients with symptoms at the time of surgery was associated with an estimated mean survival penalty of 8.3 months (95% CI: 2.5-11.9, P = 0.003). Even more impressively, when compared with patients operated on without any triggers, operating on patients with a LVEF <60% at the time of AVR was associated with an estimated mean survival penalty of 11.4 months (95% CI: 3.1-17.9, P = 0.005) after 10 years.

4. DISCUSSION

The current work investigated long-term postoperative survival of HGSAS patients from a large multicenter cohort according to American Heart Association/American College of Cardiology Class I triggered interventions. The relevant findings were (**Central Illustration**):

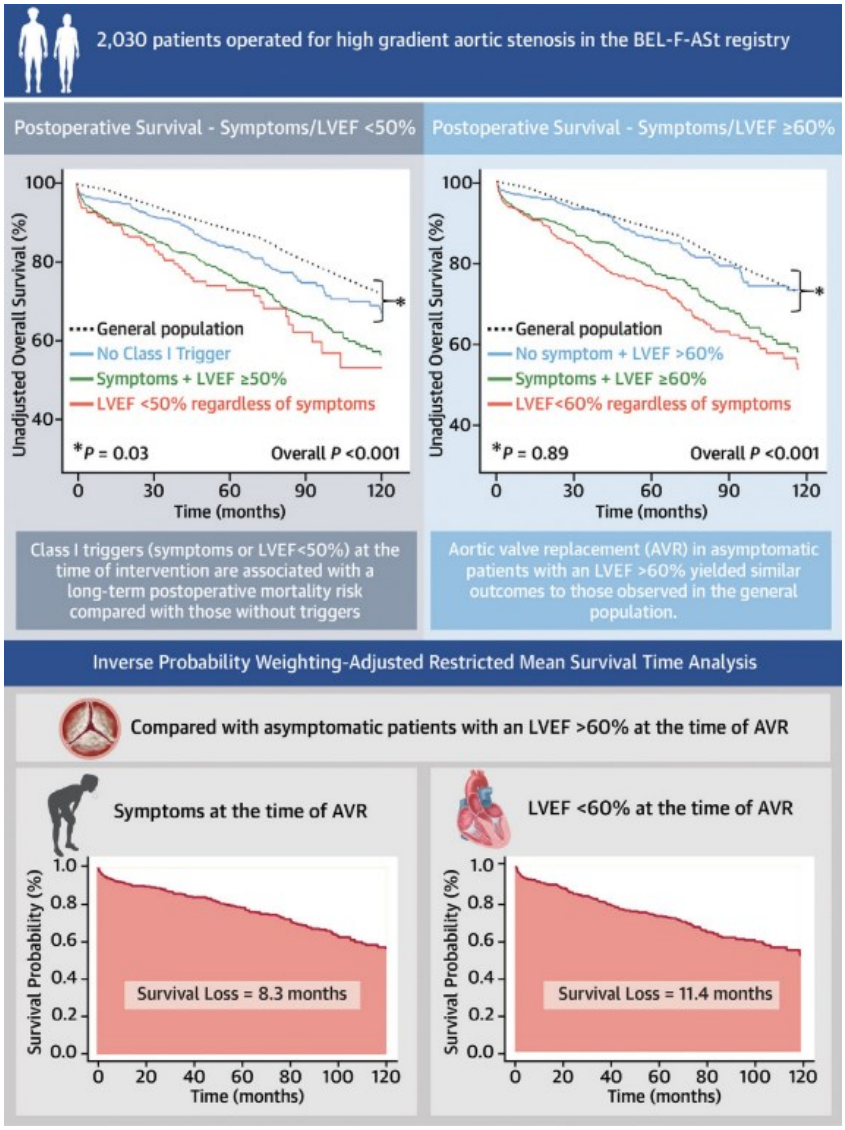
1. Class I trigger presence (ie, symptoms or LVEF <50%) at the time of intervention in HGSAS patients was deleterious, followed by an increased long-term postoperative mortality risk compared with those without triggers (about 45% more postoperative death risk vs no trigger at 10 years).

2. An LVEF <60% at the time of AVR was already associated with a 10-year postoperative survival penalty while performing AVR in asymptomatic HGSAS patients with an LVEF >60% produced similar outcomes to the general population.

3. Symptomatic patients or those with LVEF <60% who underwent AVR had a 8.3- and 11.4-month survival loss, respectively, after 10 years and compared with those operated on without symptoms and a LVEF >60%.

Controversy regarding the surgical correction timing for severe asymptomatic AS still exists [(226)] despite compelling data establishing a

better outcome in operated patients at an earlier time compared with those who experienced a watchful waiting strategy [197,227]. While data on the natural disease history already represent a strong argument for proposing early intervention, our work exclusively focused on postoperative survival reinforces the message that waiting for symptoms or LV dysfunction should be restricted. Indeed, the existing practice of deferring AVR until symptoms or LV dysfunction occur lead to rescue surgery as it is accompanied by a postoperative survival penalty for the patient. Therefore, the optimal surgical timing must be prior to trigger onset.



Central illustration: Survival Loss Associated with Late Therapeutic Indication in High-Gradient Severe Aortic Stenosis. Delaying AVR for HGSAS patients until symptoms or left ventricular dysfunction onset has a negative impact on long-term postoperative survival. Patients without class I triggers (blue line) had better survival rates than symptomatic patients with preserved LVEF (green line) and patients with reduced LVEF (red line), regardless of LVEF-threshold. AVR did not restore normal life expectancy in

asymptomatic patients with LVEF <60%. However, asymptomatic patients with LVEF >60% had similar survival rates to the general population (dotted black line). AVR in patients with symptoms or LVEF <60% resulted in 8.3- and 11.4-month survival losses, respectively, after 10 years compared to those operated on without symptoms and with LVEF >60% (P < 0.001). AVR ¼ aortic valve replacement; HGSAS = high-gradient severe aortic stenosis; IPW = inverse probability weighting; LVEF = left ventricle ejection fraction; RMST = restricted mean survival time.

PREOPERATIVE SYMPTOMS AND POSTOPERATIVE SURVIVAL. When SAS is accompanied by symptoms, AVR is recommended because of its well-established dismal outcome (>50% mortality within 3 years) in unoperated patients. Thus, despite the absence of data from a randomized clinical trial, symptomatic SAS is considered as a class I trigger for AVR by professional organizations [4,5]. Nevertheless, a substantial number of patients with severe AS deny symptoms for many years, by subconsciously reducing their activity level, thereby masking their true symptoms or exercise intolerance [226]. In addition, some patients may disavow or downplay their symptoms out of fear or anxiety regarding therapeutic interventions. Thus, physicians frequently face difficulties in treating AS patients, especially the older ones claiming to be asymptomatic. A supervised stress-test may unmask symptoms. Indeed, international guidelines recommend exercise testing in asymptomatic SAS patients [4,5], but it is only performed in a small portion of eligible HGSAS patients. Besides the fact that stress testing is underused in routine practice, it is more alarming to note that 48% of the patients referred for AVR already had severe symptoms and that 12% were hospitalized for acute heart failure [34]. Moreover, the ability of exercise testing to predict symptom onset and outcomes at 1 year is poor (positive predictive value of 55%-65%) and based on small patient's series [211,212]. Furthermore, exercise tests can only be performed by relatively young patients, which do not reflect the usual AS population age [211]. Our data suggest that waiting for symptoms in HGSAS cases is accompanied by survival loss. Thus, based on the principle that preemptive AVR can only be justified when there is clear

evidence that it actually improves long-term survival (with an acceptable perioperative risk) compared with periodic clinical reassessment until symptoms onset, our data and those from other studies [8,227] support earlier intervention strategies.

LEFT VENTRICULAR DYSFUNCTION AS A PREDICTOR OF OUTCOMES. LVEF is generally used as a surrogate of LV systolic function and is recognized as a Class I trigger for AVR when <50% in SAS [4,5]. However, the best EF threshold remains largely debated. Recently, data have shown that treatment benefits can be expected in asymptomatic HGSAS patients regardless of their EF, thus questioning the need for an EF threshold recommending AVR [156,197,198,228]. In AS, the calcified aortic valve creates an obstacle hampering the LV outflow, prompting a compensatory response for hypertrophic LV remodeling caused by the addition of sarcomeres in parallel. This adaptive mechanism aims to mitigate wall stress and sustain adequate cardiac output. Consequently, LVEF may appear preserved despite underlying reduced contractility and therefore fails to accurately reflect the underlying ongoing cardiac damage. Decreased contractility can be identified in 68% of patients at the time of diagnosis of SAS [229,230]. When compensatory mechanisms are exhausted, LVEF decreases and normal LV function recovery after AVR may not be complete. Furthermore, due to these mechanisms, LV dysfunction defined by an LVEF <50% occurs very late in the AS natural history, and at this stage, patients are rarely asymptomatic [214]. Structural myocardial changes can be identified before LVEF declines, may persist after AVR, and are independently associated with poor outcomes [100,117]. Although new risk indices such as global longitudinal strain, replacement fibrosis, and specific biomarkers are highly desirable and could radically transform the existing clinical decision paradigm [210], it must be acknowledged that they are not widely used in routine clinical practice and highly depend on local expertise [229]. Moreover, the limited accessibility and high cost of certain examinations limit their broader utilization. Thus, LVEF remains the only imaging parameter used by clinicians to propose or delay AVR in SAS patients. In line with previous research [156], our study confirms

that there is already a postoperative survival penalty when the LVEF is below 60%. Our findings provide a crucial prognostic factor, indicating that operated asymptomatic patients with an LVEF >60% experienced a survival prognosis close to that of the general population. These findings prompt the inquiry regarding the necessity of establishing a LVEF threshold for advocating an intervention. This could be evaluated in controlled randomized trial.

OPERATING HGSAS EARLIER. As aforementioned, performing surgery on HGSAS patients earlier in the disease stage (ie, asymptomatic and with an LVEF >60%) is only justified if the operative mortality is low (1.8% in our series, mean age: 74 years), and if the intervention improves the outcomes. To date, 2 randomized controlled trials have compared the "early AVR strategy" with the "watchful waiting strategy" for asymptomatic SAS patient management [(215,216)] and these studies support an early interventional approach. However, the patients included were not necessarily those encountered in clinical routine, as they were on average 7 years younger than the patients in our study. It should be emphasized that these studies showed the superiority of the 'early intervention' approach after a relatively short follow-up period. Our study highlighted the late persistent survival penalty associated with waiting for symptoms onset before AVR. We can assert that when considering the collective evidence, earlier interventions will likely become more common in the future. This trend has already been observed in our study including data from the last 2 decades (**Figure 2**). Ultimately, adopting an earlier interventional approach relies on the durability of valve substitutes and therapeutic option availability for patients in the event of reintervention. Indeed, AVR in asymptomatic patients will undoubtedly be accompanied by a repeat valve procedure increase. In this regard, the transcatheter valve-in-valve technique has a promising potential.

STUDY LIMITATIONS. The study has several limitations that should be acknowledged. Because follow-up data were obtained retrospectively, this study presents the limitations inherent to this type of analysis. First, the

indications for AVR could not be identified in all patients with no Class I indication. Secondly, biomarkers were only available in a limited number of patients (n = 690) (**Supplemental Table 5**), natriuretic peptides being unavailable in the early 2000s. As observed in many European countries, we could not provide information regarding exercise testing in asymptomatic patients [(34)] or data regarding global longitudinal strain. Despite completeness of our follow-up data and using sophisticated statistical methods like IPW to reduce biases, our patients were not randomized between early surgery and active surveillance. Accordingly, we cannot exclude unaccounted confounding factors contributing to our results. Prospective, randomized trials with long follow-up would undoubtedly provide a more definite demonstration of the superiority of early AVR vs "waiting Class I triggers."

Supplemental Table 5: BNP level among the 3 study groups.

	ALL	**No Class I trigger**	**Symptoms + EF>50%**	**EF<50%**	P overall	P1vsP2	P1vsP3	P2vsP3	N
BNP (pg/mL) Mean +/- SD	172 [73;402]	140 [55;270]	172 [77;404]	633 [327;1384]	<0.001	0.003	<0.001	<0.001	690

Natriuretic peptides were available in a limited number of patients (n=690). As expected, we observed a significant increase in BNP-levels with symptoms and/or LVEF<50%.

5. CONCLUSIONS

This large international cohort of patients who underwent AVR for HGSAS provides new crucial insights for the SAS patient management. IPW matching revealed the intrinsic implications of surgical indications, as waiting for Class I triggers onset before performing surgery on HGSAS patients was associated with a definite postoperative survival penalty compared with operated patients without any triggers. These data should encourage clinicians to adopt an early surgical strategy in HGSAS patients for whom AVR can be safely offered. Performing AVR in asymptomatic HGSAS patients with LVEF >60% produced similar outcomes to those observed in the general population whereas operating asymptomatic patients with LVEF <60% did not. This questions the need for an EF threshold recommending AVR in HGSAS patients.

6.3. STUDY 3: Atrial fibrillation in severe aortic stenosis: Impact on patients' mortality and referral to treatment.

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UNPUBLISHED DATA

ABSTRACT

BACKGROUND: Atrial fibrillation (AF) frequently coexists with severe aortic stenosis (SAS). However, it remains controversial whether AF directly contributes to adverse outcomes as a causal factor or serves more as a marker of advanced cardiac disease. Furthermore, while AF is currently not considered a guideline trigger for aortic valve replacement (AVR), it can influence the assessment of AS severity and interfere with the clinical decision to recommend AVR.

METHODS: Using the Bel-F-ASt international registry, we evaluate the impact of AF on pre- and post-operative all-cause mortality and on the referral rate for AVR in patients with SAS. We included 3463 patients (77±10 years, female 52%) with SAS and preserved ejection fraction in this study. Cox regression analysis was used to compare 5-year survival and identify predictors for AVR referral. The magnitude of the benefit of AVR according to rhythm was assessed using a time-dependent Cox model with interaction.

RESULTS: Sinus rhythm (SR) was present in 76.2% of patients, while AF was present in 23.8%. AVR was performed in 75% of patients. During a median follow-up of 37 months, AF patients had consistently worse survival than SR patients, regardless of whether they underwent AVR (23.6% vs. 36.4% and 75.4% vs. 82.0% for unoperated and operated patients, respectively; p<0.001). After adjustment for time-dependent AVR and relevant variables, AF remained associated with a worse prognosis (HR: 1.21 [1.01-1.45]; p=0.042). Both AF and SR patients benefited from AVR (HR: 0.24 [0.20-0.30]; p<0.001) to a similar extent (p=0.717). However, AVR was performed less frequently in AF patients than in SR patients (72.3% vs. 85.4%; p<0.001). Even after adjustment for other clinical and imaging factors influencing referral, including symptoms and transvalvular gradients, AF remained an independent predictor of reduced referral to AVR (HR: 0.78 [0.70-0.86]; p<0.001).

CONCLUSION: AF is an independent marker of poor prognosis in SAS. Furthermore, AF patients are less frequently referred for AVR, even though they benefit from AVR as much as SR patients. Assessing the functional impact of AF in SAS patients is challenging, and treatment strategies should be evaluated in further prospective studies to aid clinical decision-making.

1. INTRODUCTION

Aortic valve stenosis (AS) affects approximately 5% of adults over the age of 65 and is the predominant form of valvular heart disease (VHD) worldwide [1,34]. Conversely, atrial fibrillation (AF) represents a prevalent form of arrhythmia, with its occurrence increasing with age to ultimately affect approximately 10% in individuals over 80 years old [1]. Previous studies have indicated that 20-40% of patients with severe AS also exhibit AF, with a higher prevalence among older individuals [231,232]. The increased occurrence of AF in AS patients may be attributed to structural changes such as ventricular hypertrophy, left atrial dilation, and fibrosis, along with the chronic rise in afterload resulting from valvular obstruction [233].

Atrial fibrillation is thought to be a significant predictor of adverse outcomes in AS in both medically and surgically managed patients, regardless of AS severity, symptoms, or cardiac remodeling [231,234-236]. This suggests the early consideration of aortic valve replacement (AVR) in severe aortic stenosis (SAS) patients with AF. However, some studies indicate that the adverse impact of AF may arise from its association with increased pulmonary pressures, left atrial dilation, and reduced left ventricular stroke volume [237,238] and/or comorbidities [239]. Therefore, AF may serve as a marker of advanced heart disease rather than a direct causal factor. In severe primary mitral regurgitation, the onset of AF is considered a Class IIa indication for intervention, regardless of symptoms, due to its association with an elevated incidence of adverse cardiac events [240,241]. However, AF onset in SAS has not been identified as a prognostic marker that may lead to an early recommendation for AVR, although AF is considered a stage 2 marker of myocardial damage [208]. Whether the onset of AF in the presence of SAS warrants consideration of AVR is a clinical question of great importance. Conflicting data exist on this matter. Some authors suggest that the benefit of AVR in reducing all-cause mortality is notably greater in AF patients compared to those in sinus rhythm (SR), regardless of symptom severity, [242] while other studies have not demonstrated a significant interaction [236,243-

[245]. It is worth noting that the coexistence of AF and SAS makes it difficult for clinicians to associate patients' symptoms with one condition or the other [237]. Moreover, in AF, the high variability of cardiac cycles often leads to reduced maximum transaortic velocities, potentially misleading clinicians regarding the true severity of AS [246]. These clinical and echocardiographic characteristics may contribute to delayed referral for treatment, thereby impacting periprocedural risk and long-term outcomes [246,247].

Given the lack of randomized trials, the only option for refining the prognostic implications of SAS with AF is to gather large registries of patients with SAS and compare outcomes after accounting for baseline characteristics. The aim of this study was to examine clinical outcomes, including rates of AVR, determinants of overall mortality, and factors influencing referral for treatment in patients with SAS who have preserved left ventricular ejection fraction (LVEF ≥50%) and coexisting AF, compared with those in sinus rhythm. We collected extensive AS registries in France and Belgium and hypothesized that AF, compared with sinus rhythm, is associated with an increased risk of mortality in SAS patients with preserved LVEF, independently of AS-induced cardiac remodeling. Furthermore, we hypothesized that AVR is beneficial for all SAS patients, regardless of atrial rhythm and symptom status, and that AF patients with SAS and preserved ejection fraction are often under-referred for AVR, despite experiencing greater symptomatic burdens.

2. METHODS

STUDY POPULATION AND DESIGN

Patients older than 18 years who were diagnosed with at least mild AS in the echocardiography laboratories of two French hospitals (Amiens and Lille) and one Belgian hospital (Brussels) between 2000 and 2020 were prospectively enrolled in the Bel-F-ASt registry. The exclusion criteria were as follows: 1) AVA ≥ 1 cm^2, 2) left ventricular ejection fraction < 50%, 3)

previous valvular surgery, 4) more than moderate aortic regurgitation, and 5) glomerular filtration rate < 30 ml/min. Cardiac rhythm was assessed using a standard 12-lead electrocardiogram at the time of the index echocardiogram. The patients were classified into two groups: sinus rhythm (N=2639, 76.2%) and atrial fibrillation (N=824, 23.8%), whether paroxysmal or permanent. Coronary artery disease (CAD) was defined as the presence of a documented history of acute coronary syndrome, coronary stenosis > 50% previously confirmed by coronary angiography, or a history of coronary revascularization. Each patient's personal cardiologist evaluated and graded symptoms based on the New York Heart Failure Association (NYHA) criteria, as well as the presence of angina or syncope. The validated Charlson comorbidity index was calculated for each patient, and the study was conducted in accordance with institutional policies and the revised Helsinki declaration.

ECHOCARDIOGRAPHY

All patients underwent a comprehensive ultrasound examination using commercially available systems, including 2D echocardiography as well as Doppler examinations. Multiple transducer positions were systematically employed to record maximal instantaneous and mean pressure gradients across the aortic valve, while AVA was calculated using the continuity equation. In patients with AF, five consecutive cardiac cycles were systematically averaged, and LV volumes and LVEF were calculated using the biplane Simpson method. LV stroke volume was determined by multiplying the LVOT area on the parasternal long-axis view by the LVOT velocity–time integral measured by pulsed-wave Doppler. Systolic pulmonary artery pressure was estimated by measuring the systolic transtricuspid pressure gradient, calculated using the modified Bernoulli equation.

FOLLOW-UP AND OUTCOMES

The indication and timing of AVR were determined by the heart team with the approval of the patient's cardiologist, in accordance with guidelines.

Clinical follow-up data were collected through direct patient interviews and telephone calls to physicians, patients, or their relatives if necessary. The study endpoints were all-cause mortality and referral to AVR from the index echocardiography up to 5 years after inclusion.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean ± standard deviation or median (interquartile range, IQR), depending on the normality of the distribution. Categorical data are expressed as numbers and percentages, with baseline differences in the continuous data among the groups being explored using the Student's t-test (for normally distributed data) or the Mann-Whitney test (for non-normally distributed data). Pearson's chi-square test was used for categorical variables. Outcomes (all-cause mortality or AVR referral at 5 years) were displayed using the Kaplan-Meier method and compared according to atrial rhythm using a two-sided log-rank test. To analyze the time to the first event, i.e., all-cause death and AVR referral within 5 years, different modeling methods were used to adjust the effect of atrial rhythm for relevant covariates. Models 1 and 2 were constructed using univariate and multivariate Cox proportional hazards regression—respectively—by censoring patients who did not first experience the event of interest. The proportional hazards assumption was confirmed using statistics and graphs based on Schoenfeld residuals. Model fit was evaluated with Martingale and Cox-Snell residuals. Model 3 (frailty model) was constructed by adding a random effect with a Gaussian distribution to the fixed effects identified in Model 2. Models 4 and 5 were built using univariate and multivariate Fine and Gray regressions, respectively, treating both outcomes as competing risks. When analyzing both pre- and post-operative survival, a multi-state Cox model was developed using AVR as a time-dependent variable. The effects of both atrial rhythm and time-dependent AVR on the risk of all-cause mortality at 5 years were estimated and adjusted for relevant covariates, with the interaction between these two variables also being assessed. No automatic stepwise selection technique was used to construct the

multivariate analyses; only the highest likelihood ratios and chi-squares of the relevant clinical variables were considered. Lastly, statistical analyses were conducted using RStudio 1.4.1106, with a P-value of <0.05 being considered statistically significant.

3. RESULTS

BASELINE CHARACTERISTICS

The study population consisted of 3463 patients with severe aortic stenosis and preserved LVEF, of whom 824 (23.8%) presented with AF (**Figure 1**). The differences in demographic and clinical characteristics between SR and AF patients are summarized in **Table 1**. Patients with SAS and AF were, on average, older (79.7 vs. 75.6 years, p<0.001) and more often symptomatic. The presence of CAD was equally distributed among the groups. AF patients more frequently suffered from diabetes and hypertension, and had a lower glomerular filtration rate. Overall, the median BNP, Charlson index, and EuroSCORE II levels were higher in the AF group. Assessment of valve stenosis severity showed that aortic valve area was quite similar in both groups (0.70 vs. 0.71 cm^2; p=0.051), but AF patients had an average 12.2% lower mean gradient (43.9 vs. 50.0 mmHg; p<0.001). AF patients had an increased LV mass index (120 vs. 113 g/m^2; p<0.001) but similar relative wall thickness, associated with a lower LVEF (62.8 vs. 64.9%; p<0.001) and a lower stroke volume index (36.6 vs. 40.1 ml/m^2; p<0.001). Only 23.4% of AF patients presented with low-flow, low-gradient AS. As expected, AF patients had a higher left atrial volume index (51.9 vs. 40.1 ml/m^2; p<0.001) as well as higher systolic pulmonary pressure.

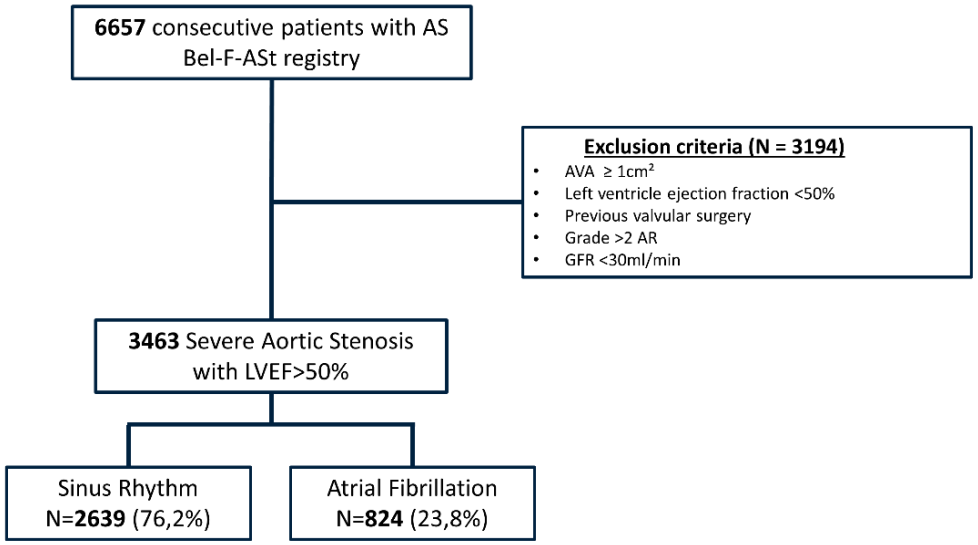

Figure 1. Flow chart illustrating case selection and classification. AR = aortic valve regurgitation; AS = aortic valve stenosis; AVA = aortic valve area; GFR = glomerular filtration rate; LVEF = left ventricle ejection fraction.

Table 1: Population characteristics.

	ALL	Sinus Rhythm	Atrial Fib.	P value
	N=3463	N=2639	N=824	
Demographic data				
Age	76.6±9.81	75.6±10.1	79.7±8.06	<0.001
Female	1786 (51.6%)	1372 (52.0%)	414 (50.2%)	0.403
BMI (kg/m^2)	27.4±5.12	27.4±5.09	27.5±5.23	0.560
BSA (m^2)	1.86±0.22	1.85±0.21	1.87±0.22	0.073
Symptoms				
NYHA Class				<0.001
I	798 (23.0%)	633 (24.0%)	165 (20.0%)	
II	1643 (47.4%)	1272 (48.2%)	371 (45.0%)	
III	832 (24.0%)	609 (23.1%)	223 (27.1%)	
IV	190 (5.49%)	125 (4.74%)	65 (7.89%)	
Angor	782 (22.6%)	629 (23.8%)	153 (18.6%)	0.002
Syncope	318 (9.18%)	232 (8.79%)	86 (10.4%)	0.174
Comorbidities				

Diabetes	907 (26.2%)	660 (25.0%)	247 (30.0%)	0.005
Hypertension	2481 (71.6%)	1849 (70.1%)	632 (76.7%)	<0.001
CAD	1612 (46.5%)	1227 (46.5%)	385 (46.7%)	0.940
GFR (mL/min)	60.0 [45.9;78.8]	61.9 [47.4;80.2]	54.3 [41.5;70.7]	<0.001
BNP (pg/mL)	168 [73.0;377]	122 [54.0;285]	297 [158;542]	<0.001
Charlson Index	4.00 [3.00;6.00]	4.00 [3.00;5.00]	5.00 [4.00;7.00]	<0.001
EuroSCORE II	1.95 [1.27;3.35]	1.92 [1.23;3.30]	2.05 [1.38;3.53]	<0.001
Echocardiographic parameters				
AVA (cm²)	0.71±0.17	0.71±0.17	0.70±0.17	0.051
Vmax (m/s)	4.34±0.78	4.40±0.76	4.14±0.80	<0.001
MG (mmHg)	48.5±17.7	50.0±17.7	43.9±17.1	<0.001
LVEDD (mm)	46.7±7.16	46.4±7.05	47.5±7.47	<0.001
LV Mass (g)	213±75.9	209±73.9	224±81.2	<0.001
LVi Mass (g/m²)	115±38.5	113±37.6	120±40.6	<0.001
RWT	0.52±0.15	0.52±0.15	0.52±0.14	0.926
LAVi (ml/m²)	43.6±17.2	40.1±14.4	51.9±20.1	<0.001
LAVi >50ml/m² (%)	604 (29.8%)	316 (22.2%)	288 (47.7%)	<0.001
E/e’	12.7±6.90	12.6±6.66	13.1±7.54	0.193
LVEF (%)	64.4±7.85	64.9±7.92	62.8±7.38	<0.001
LVOT SV (ml)	72.4±19.0	73.9±18.5	67.9±19.9	<0.001
SVi (ml/m²)	39.2±9.93	40.1±9.65	36.6±10.3	<0.001
SVi <35ml/m²	1273 (36.8%)	878 (33.3%)	395 (47.9%)	<0.001
Zva (mmHg/mL/m2)	5.07±1.48	4.98±1.41	5.37±1.66	<0.001
sPAP (mmHg)	33.3±11.5	31.6±10.3	38.6±13.1	<0.001
sPAP >45 mmHG	404 (11.7%)	222 (8.41%)	182 (22.1%)	<0.001
AR2	159 (4.59%)	132 (5.00%)	27 (3.28%)	0.049
TR>1	88 (2.54%)	44 (1.67%)	44 (5.34%)	<0.001

Values are n (%), %, or mean ± SD.

Abbreviations: AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; BMI = body mass index; BNP = brain natriuretic peptide; BSA = body surface area; CAD = coronary artery disease; EF = ejection fraction; GFR = glomerular filtration rate; LVAi = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; MG = mean gradient; sPAP = systolic pulmonary artery pressure; RWT = relative wall thickness; SVi = indexed stroke volume; TR = tricuspid regurgitation; Vmax = maximal transvalvular velocity; Zva = valvulo-arterial impedance.

NATURAL HISTORY OF AS-PATIENTS WITH AF

During a median follow-up of 37 months (interquartile range: 17-60), 849 (24.5%) deaths occurred, of which 470 (13.6%) were observed before referral for AVR, with a higher mortality rate in AF patients than in SR patients (23.7% vs. 10.4%, respectively, p<0.001). The 5-year survival rate, with censoring at the time of AVR, was 29.1% for AF patients and 45.4% for SR patients (LogRank P<0.001) (**Figure 2A**). When considering AVR as a competing risk event, AF patients had a 5-year survival rate of 72.5%, compared to 87.6% for SR patients (LogRank P<0.001) (**Figure 3**). Not surprisingly, according to univariable Cox regression analysis (**Table 2**), age, comorbidities, LVEF, pulmonary pressure, and indexed stroke volume were predictors of mortality, along with AF. In univariate analysis, AF was associated with an increased risk of all-cause mortality when accounting for AVR as a censoring or competing risk event (HR: 1.79 [1.49-2.15] and HR: 2.48 [2.10-2.94], respectively**, Table 3, Models 1 & 2**). Based on the results of the univariate analysis, two different regression techniques were employed to develop two distinct models (Cox and Fine & Gray models) that accounted for eight relevant covariates: age, body mass index, NYHA class, diabetes, coronary artery disease, aortic valve area, left atrial volume index, and left ventricular ejection fraction. After adjustment, AF emerged as an independent predictor of all-cause mortality in both models (HR: 1.25 [1.01-1.54] and HR: 1.23 [1.02-1.49], respectively) (**Table 3, Models 3 & 4**). The 5-year adjusted survival rates were 48.4% in AF patients compared to 52% in SR patients (P = 0.039, Figure 2B). Finally, when incorporating a random effect to account for patient-level risk variations (P=0.011), AF patients appeared to have a 31% increased risk of all-cause mortality compared to SR patients (P = 0.033) (**Table 3, Model 5**).

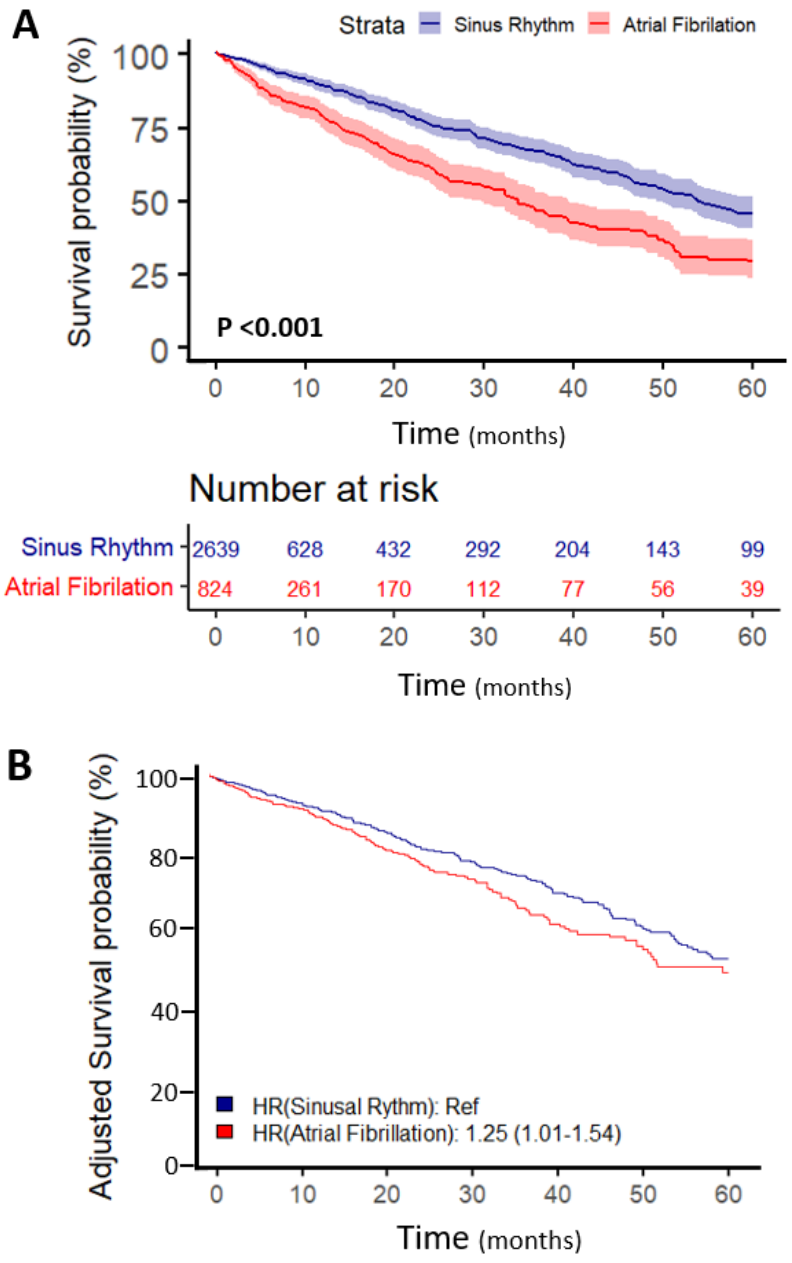

Figure 2. 5-year unadjusted risk of all-cause mortality (A) and 5-year adjusted risk of all-cause mortality (B) in AS patients according to cardiac rhythm. Patients were censored at the time of aortic valve replacement.

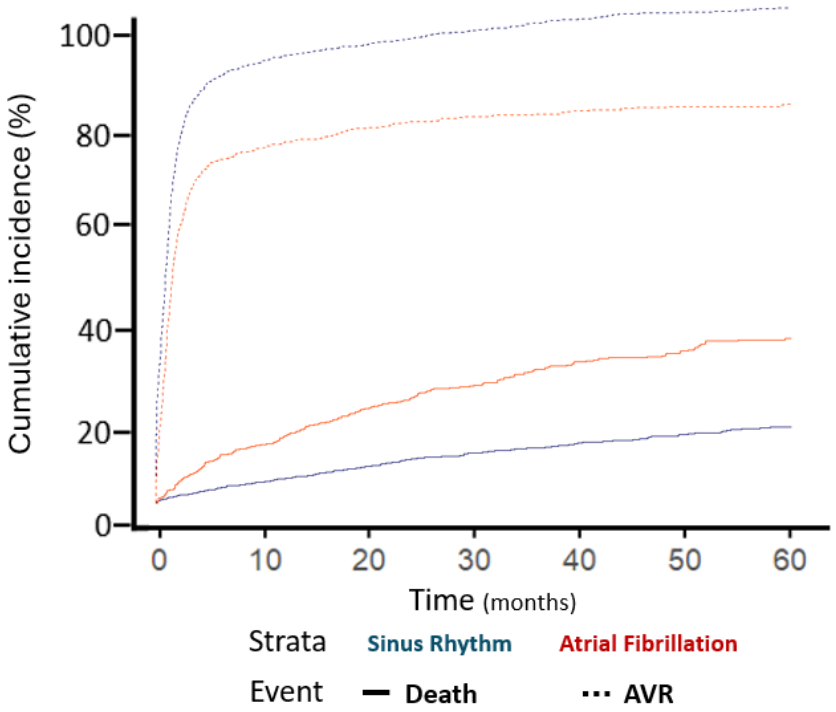

Figure 3. 5-Year Unadjusted Cumulative Incidence of Competing Events: All-Cause Death and Aortic Valve Replacement by Atrial Rhythm. Solid line = all-cause death; dashed line = AVR. The blue lines correspond to patients in sinus rhythm, and the red lines correspond to patients with atrial fibrillation.

Table 2: Univariate Cox regression analysis for 5-Year all-cause mortality.

Risk of 5-Year Mortality	HR	95% CI	P value
	Univariate Cox Models		
Age by 5	1.43	1.34-1.51	<0.001
Gender	1.14	0.94-1.37	0.187
BMI (kg/m²)	0.96	0.94-0.98	<0.001
BSA (m²)	0.38	0.25-0.58	<0.001
NYHA Class	1.49	1.36-1.64	<0.001
Diabetes	1.20	0.98-1.46	0.081
Hypertension	1.21	0.97-1.50	0.091
CAD	0.88	0.73-1.08	0.217
AF	1.79	1.49-2.15	<0.001
GFR (mL/min)	0.98	0.98-0.99	<0.001
Charlson Index	1.17	1.13-1.22	<0.001
AVA (cm²)	0.17	0.10-0.29	<0.001
MG (mmHg)	1.00	0.99-1.01	0.48
Vmax (m/s)	1.04	0.93-1.17	0.483
LV Mass index (g/m²)	1.00	0.99-1.01	0.357
RWT	3.03	1.63-5.62	<0.001
LAVi (ml/m²)	1.02	1.01-1.02	<0.001
LVEF (%)	0.98	0.97-0.99	0.003
SVi (ml/m²)	0.98	0.97-0.99	<0.001
Zva (mmHg/mL/m2)	1.10	1.05-1.16	<0.001
sPAP >45	1.81	1.43-2.29	<0.001
AR2	1.34	0.88-2.04	0.173
MR>1	0.84	0.34-2.03	0.696
TR>1	0.91	0.38-2.19	0.828

Abbreviations: AF = atrial fibrillation; AR2 = aortic regurgitation grade 2; AVA = aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; GFR = glomerular filtration rate; LAVi = left atrial volume index; MG = mean gradient; MR = mitral regurgitation; sPAP = systolic pulmonary artery pressure; RWT = relative wall thickness; SVi = indexed stroke volume; TR = tricuspid regurgitation; Vmax = maximal transvalvular velocity; Zva = valvulo-arterial impedance.

Table 3: 5-Year risk of either mortality or referral for aortic valve replacement as a function of AF according to various models.

5-Year Risk of Event associated with Atrial Fibrillation									
		Mortality				Referral for AVR			
		HR	95%CI	P-value	C-index	HR	95%CI	P-value	C-index
AF	Model 1	**1.79**	1.49-2.15	0.001	0.58	**0.67**	0.61-0.74	<0.001	0.54
	Model 2	**2.48**	2.10-2.94	<0.001	0.60	**0.64**	0.59-0.70	<0.001	0.54
	Model 3	**1.25**	1.01-1.54	0.039	0.72	**0.78**	0.70-0.86	<0.001	0.69
	Model 4	**1.23**	1.02-1.49	0.032	0.77	**0.76**	0.69-0.83	<0.001	0.69
	Model 5	**1.31**	1.06-1.62	0.033	0.83	**0.76**	0.69-0.85	<0.001	0.73

Legend:

Model 1: Unadjusted Cox model.

Model 2: Unadjusted competing risk model.

Model 3: Cox model adjusted for Age, BMI, NYHA class, Diabetes, CAD, AVA, LAVi, LVEF for death event and Age, Sex, BMI, NYHA class >1, HTA, Charlson index, CABG, AVA, LVEF, SVi <35, High gradient status, sPAP >45, MR>1 or TR>1 for AVR referral.

Model 4: Competing risk model adjusted for the same covariates as Model 3.

Model 5: Cox model adjusted for the same covariates as Model 3 for the fixed effects + additional random effects with Gaussian distribution.

Abbreviations: **see Table 2.**

OVERALL MORTALITY WITH TIME-DEPENDENT AVR ANALYSIS

When pre- and post-operative mortality were considered, patients with AF had consistently worse 5-year prognoses than patients with SR, regardless of whether they had undergone AVR (23.6% vs 36.4% and 75.4% vs 82.0%; P <0.001, respectively for unoperated on and operated on patients) **(Figure 4, A)**. Peri-operative mortality (defined as death occurring within the first 30 days after AVR) occurred in 71 (2.7%) patients. The incidence of these perioperative deaths was similar between the groups (p=0.711).

In bivariate analysis of the risk of overall mortality at 5 years, AF was associated with an increased risk (HR: 1.66 [1.44-1.92]), while time-dependent AVR was associated with a strong protective effect (HR: 0.32 [0.28-0.38]) **(Table 4)**. In multivariate analysis, AF remained an independent predictor of outcome after adjustment for age, body mass index, NYHA class, diabetes, aortic valve area, left atrial volume index, LVEF, and systolic pulmonary arterial pressures >45 mmHg. 5-year survival rates for AF and SR patients were 52.5% vs 56.0%, respectively, after adjustment (P = 0.042) **(Figure 4, B)**. The magnitude of the protective effect of AVR increased following multivariate adjustment (HR: 0.24 [0.20-0.30]), however irrespective of cardiac rhythm, the protective effect of AVR remained consistent (P for interaction = 0.717). Notably, AF patients did not experience a lesser benefit from AVR compared to SR patients **(Table 4)**.

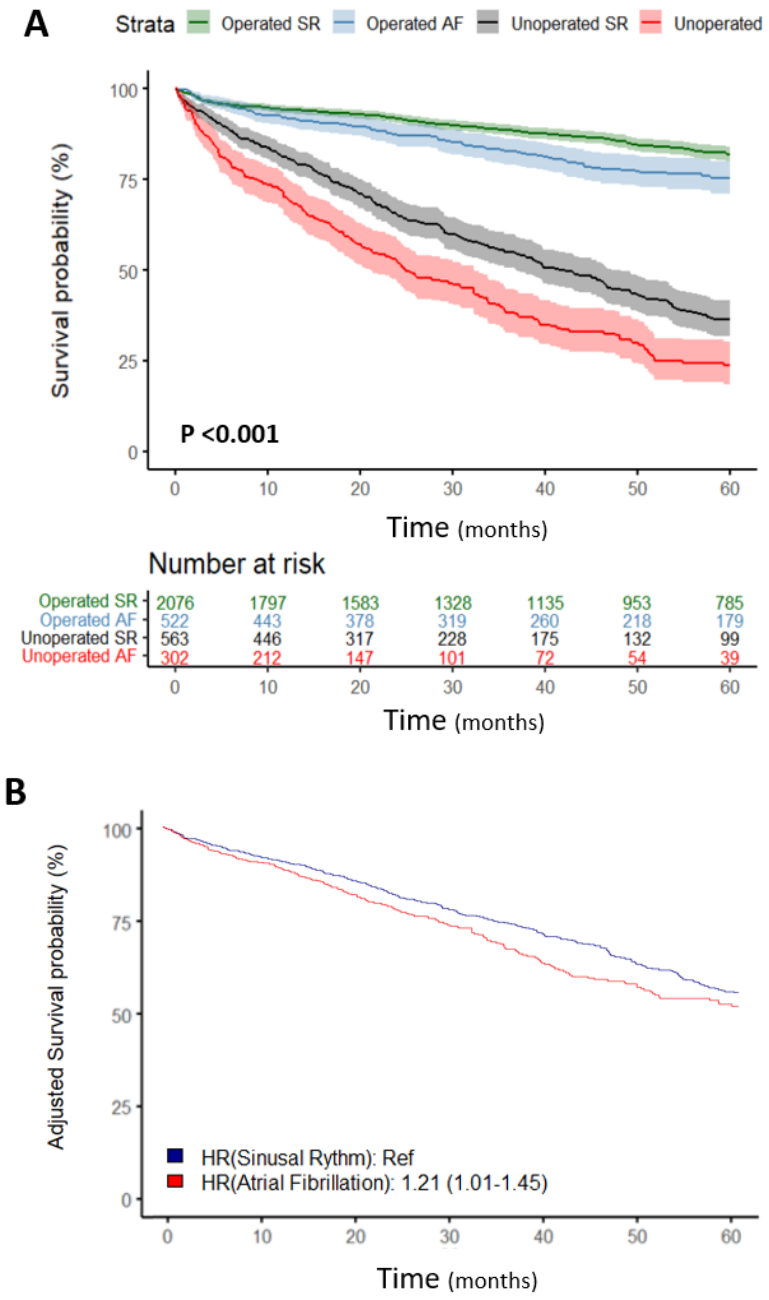

Figure 4: 5-Year All-Cause Mortality Stratified by Atrial Rhythm and AVR Status (A). 5-Year Adjusted Pre- and Post-Operative Mortality Curves with AVR as a Time-Dependent Variable (B).

Table 4: Associations of Clinical Risk Factors with 5-Year Mortality Risk and AVR as a Time-Dependent Variable

Risk of 5-Year Mortality	Bivariate Cox Models: Time-dependent AVR + 1 covariate			Multivariate Cox Model		
	HR	95% CI	P value	HR	95% CI	P value
Age by 5	1.39	1.32-1.45	<0.001	1.28	1.21-1.36	<0.001
Female	1.03	0.90-0.18	0.655			
BMI	0.96	0.95-0.98	<0.001	0.97	0.95-0.99	0.003
BSA	0.48	0.35-0.66	<0.001			
NYHA Class	1.44	1.34-1.56	<0.001	1.30	1.18-1.43	<0.001
Diabetes	1.24	1.07-1.43	0.005	1.33	1.10-1.61	0.003
HTA	1.22	1.04-1.43	0.013			
CAD	1.07	0.93-1.23	0.357			
Cockroft	0.98	0.98-0.99	<0.001			
Charlson Index	1.18	1.14-1.21	<0.001			
AVA	0.29	0.19-0.44	<0.001	0.55	0.32-0.94	0.028
Mean Gradient	0.99	0.98-0.99	0.005			
Index LV Mass	1.00	0.99-1.00	0.774			
RWT	1.77	1.10-2.88	0.020			
LAVi	1.02	1.01-1.02	<0.001	1.01	1.00-1.01	0.001
LVEF	0.98	0.97-0.99	<0.001	0.99	0.98-1.00	0.067
SVi	0.98	0.97-0.98	<0.001			
Zva	1.12	1.07-1.17	<0.001			
sPAP >45	1.95	1.65-2.32	<0.001	1.41	1.14-1.72	0.001
Grade 2 AR	1.24	0.91-1.68	0.172			
Grade 2 MR	1.35	0.88-2.09	0.172			
Grade >1 TR	1.39	0.90-2.14	0.139			
	Time-dependent AVR + AF					
Time-dep. AVR	0.32	0.28-0.38	<0.001	0.24	0.20-0.30	<0.001
Atrial Fibrillation	**1.66**	1.44-1.92	<0.001	**1.21**	1.01-1.45	0.042
Interaction			**0.199**			**0.717**

Abbreviations: AR2 = aortic regurgitation grade 2; AVA = aortic valve area; BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; GFR = glomerular filtration rate; LAVi = left atrial volume index; MG = mean gradient; MR = mitral

regurgitation; sPAP = systolic pulmonary artery pressure; RWT = relative wall thickness; SVi = stroke volume index; TR = tricuspid regurgitation; Vmax = maximal transvalvular velocity; Zva = valvulo-arterial impedance.

AVR REFERRAL AND ATRIAL RHYTHM

AVR was performed in a large proportion of the overall cohort (N=2598; 75.0%) and was mainly surgical (N=2282; 87.9%). The 5-year AVR referral rate, with censoring when death occurred before intervention, was 72.3% for AF and 85.4% for SR (Log Rank P<0.001). When considering death as a competing risk event, patients with AF had a 5-year referral rate of 65.3% compared to 81.0% for SR patients (Log Rank P<0.001) (**Figure 3**). The median time from inclusion to AVR was also significantly longer in the presence of AF (1.33 vs. 1.05 months; P<0.001). At one month from inclusion, 50% more patients had undergone AVR if they were in SR compared to AF patients. This large disparity in proportions fell to 33% at 2 months and persisted to the extent of 22% at 6 months (57.8% vs. 70.4%; P<0.001). Notably, concomitant coronary artery bypass was also less frequently needed in AF patients (14.4% vs. 22.1%; P<0.001).

In univariate analysis, AF was associated with a decreased AVR referral when accounting for death as a censoring or competing risk event compared with SR patients (HR: 0.67 (0.61-0.74) and HR: 0.64 (0.59-0.70), respectively) **(Tables 5 and 3, Models 1 & 4)**. Based on the results of the univariate analysis, two different regression techniques were employed to develop two models incorporating the same fourteen covariates: age, female sex, body mass index, NYHA class, hypertension, need for CABG, Charlson index, aortic valve area, mean gradient >40 mmHg, LVEF, stroke volume index <35 ml/m², systolic pulmonary pressures >45 mmHg, and significant MR or TR. Following adjustment, AF remained independently associated with reduced referral in both models (Cox and Fine & Gray) (HR: 0.75 (0.67-0.83) and HR: 0.73 (0.66-0.80), respectively) **(Tables 5 and 3, Models 2 & 5)**. The adjusted 5-year AVR referral rates were 45.3% in AF patients compared to 56.2% in SR patients (P

<0.001). When adding a random effect to account for patient-level risk variations (P = 0.087), AF patients appeared to have a 27% reduction in AVR referral despite SAS compared to SR patients (P <0.001) **(Table 3, Model 3)**.

Table 5: Associations of Clinical Risk Factors with 5-Year Risk of Aortic Valve Replacement.

Risk of 5-Year AVR	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
	Univariate Cox Models			Multivariate Cox Model			Multivariate Fine & Gray Model		
Age by 5	0.93	0.92-095	<0.001	0.97	0.95-0.99	0.012	0.96	0.94-0.98	<0.001
Female	0.81	0.75-0.87	<0.001	0.82	0.76-0.89	<0.001	0.84	0.77-0.91	<0.001
BMI	1.03	1.02-1.03	<0.001	1.02	1.01-1.03	<0.001	1.02	1.02-1.03	<0.001
NYHA Class >1	1.26	1.21-1.32	<0.001	1.88	1.70-2.09	<0.001	1.82	1.66-2.00	<0.001
Diabetes	0.95	0.87-1.03	0.228						
HTA	0.89	0.82-0.97	0.009	0.91	0.84-0.99	0.046	0.92	0.84-0.99	0.043
Need for CABG	2.00	1.83-2.19	<0.001	2.30	2.10-2.52	<0.001	2.37	2.17-2.59	<0.001
Atrial Fibrillation	0.67	0.61-0.74	<0.001	**0.78**	0.70-0.86	<0.001	0.76	0.69-0.83	<0.001
Cockroft	1.01	1.00-1.01	<0.001						
Charlson Index	0.93	0.91-0.95	<0.001	0.96	0.93-0.98	<0.001	0.96	0.93-0.98	<0.001
AVA	0.21	0.17-0.27	<0.001	0.22	0.16-0.29	<0.001	0.24	0.18-0.32	<0.001
MG>40 or PV>4	2.46	2.22-2.72	<0.001	1.72	1.53-1.93	<0.001	1.70	1.52-1.89	<0.001
RWT	2.28	1.74-2.97	<0.001						
LAVi	1.00	1.00-1.00	0.683						
LVEF	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	<0.001	1.02	1.01-1.03	<0.001
SVi <35	0.87	0.80-0.94	<0.001	0.82	0.75-0.91	<0.001	0.83	0.75-0.91	<0.001
sPAP >45	0.83	0.74-0.95	0.004	0.86	0.75-0.98	0.024	0.83	0.74-0.93	0.002

Grade >1 MR	1.83	1.46-2.30	<0.001	1.49	1.17-1.89	0.001	1.51	1.20-1.99	0.001
Grade >1 TR	1.38	1.10-1.75	0.006	2.06	1.60-2.65	<0.001	2.11	1.66-2.69	<0.001

Abbreviations: AVA = aortic valve area; BMI = body mass index; CAD = coronary artery disease; LVEF = ejection fraction; GFR = glomerular filtration rate; LVAi = left atrial volume index; MG = mean gradient; MR = mitral regurgitation; sPAP = systolic pulmonary artery pressure; RWT = relative wall thickness; SVi = indexed stroke volume; TR = tricuspid regurgitation.

4. DISCUSSION

This study evaluated the impact of atrial fibrillation on all-cause mortality and the referral rate for AVR in a large multicenter cohort of patients with severe AS and preserved ejection fraction. The key findings are as follows:

1. In the presence of a severe AS, AF patients have consistently worse survival rates than SR patients, regardless whether they have undergone AVR or not.
2. While both AF and SR patients benefit from AVR to a similar degree, AVR is systematically performed less frequently in AF patients than in SR patients. Even following adjustment for other clinical and imaging factors influencing referral including symptoms and transvalvular gradients, AF remains an independent predictor of reduced referral to AVR.

Currently, treatment guidelines for SAS do not incorporate AF into treatment decisions. Our study thus highlights the need to consider this parameter in the management of these patients. Further, efforts must be made to avoid delaying treatment, since AF patients benefit just as much from it as patients with sinus rhythm.

AF: an actor or a marker of advanced disease in AS patients?

Severe AS significantly prompts individuals to develop AF, as evidenced by its high prevalence (around 24%) in our study cohort. The development of AF is primarily attributed to LV hypertrophy, resulting in a chronic elevation in LV filling pressures, which leads to left atrial dilatation and fibrosis—key determinants of AF [(248)]. AF may therefore reflect maladaptive responses of the left atrium to increased afterload in AS, indicating ongoing myocardial damage [(208)]. However, AF may also be viewed as an independent condition that contributes to adverse outcomes. Atrioventricular desynchronization in AF impairs ventricular filling and diminishes cardiac output, negatively affecting patient prognosis. Additionally, AF contributes to left atrial enlargement, which is a significant predictor of mortality in patients with severe AS [(11)].

The coexistence of AS and AF reasonably leads to an expectation of increased overall mortality. However, the exact contribution of AF to mortality remains unclear: is AF a contributor or merely a marker of advanced heart disease? In this study, we adjusted for various markers of valvular and myocardial severity to elucidate this question. We adjusted the effect of AF with AS severity using the AVA rather than gradients or velocities, which are strongly influenced by RR interval variability [(247)]. Furthermore, adjustment for LA volume, LVEF, and systolic pulmonary pressures highlighted the independent prognostic impact of AF, given its frequent association with these factors. Our findings underscore the detrimental impact of AF on outcomes in patients with SAS and provide support for the assertion that AF is as much a contributor as a marker of advanced disease in SAS patients.

Benefit of AVR in AF

Given that atrial fibrillation commonly coexists with indicators of advanced heart disease such as myocardial hypertrophy, decreased ejection fraction, and elevated pulmonary pressures, one might anticipate diminished

benefits from AVR in these patients. However, although post-operative survival rates are lower in AF patients than those with SR, they still derive significant benefits from AVR that do not differ from those of SR patients. Several factors could potentially explain this post-operative survival penalty, which cannot be solely attributed to AF. Firstly, AF is frequently linked with adverse myocardial remodeling, which carries independent prognostic implications. Secondly, AF patients experience delayed referral to AVR, potentially contributing to the observed difference in survival. Adjusting for the timing of AVR helps mitigate this effect, reducing the hazard associated with AF. Finally, reduced inverse remodeling following AVR is anticipated in AF patients, which is supported by findings from Ledwoch et al. demonstrating that AF independently correlates with a lower likelihood of improvement in the left ventricular mass index one year following AVR compared to patients in sinus rhythm. This reduced remodeling was associated with an increased risk of combined death and rehospitalization. [249].

Reduced referral rate to AVR

Another important finding is the reduced rate and delayed timing of intervention in AF patients, despite their higher prevalence of symptoms and adverse cardiac remodeling. Confirming the true severity of AS is crucial; however, in the context of AF, it is hindered by the inherent irregularity of cardiac cycles. The variability in stroke volume between cycles and averaging over multiple beats may result in the underestimation of true transvalvular velocities [246]. Consequently, AF patients often fail to meet conventional thresholds for severity (i.e. peak velocities > 4m/s or mean gradient > 40mmHg), reducing the likelihood of undergoing AVR, as observed in patients with low gradient severe AS [246]. Current guidelines recommend AVR as a Class IIa indication in symptomatic patients with low-flow low-gradient AS with preserved EF. However, this recommendation does not apply to the majority of AF patients. Despite AF being a classic provider of low stroke volume, only 23.4% of AF patients in our study exhibited low-

flow, low-gradient AS, and merely 17.6% were symptomatic with a NYHA functional class >1. These data illustrate the difficulties clinicians face when confronted with patients presenting with both AS and AF. Calcium score, as well as stress tests or natriuretic peptide measurements, could also be valuable in the decision-making process for operating on patients with both AS and AF. Nevertheless, our data support the notion that AF could be considered a trigger for surgery, which should be evaluated in prospective studies.

Limitations

The study has several limitations that should be acknowledged. Since the follow-up data were obtained retrospectively, this study carries the inherent limitations of this type of analysis, particularly concerning confounding bias. We lacked information on the follow-up of atrial rhythm over time, and therefore on the proportion of new-onset AF, as well as on the prognostic impact of restoration of sinus rhythm after AVR, which limits the conclusions that can be drawn. Furthermore, we did not distinguish between paroxysmal and permanent AF, and the results could differ for the two subtypes. We also lacked information on medications, which is particularly important for anticoagulation, as it is known to affect outcomes in patients with AF. We could not provide information regarding exercise testing in asymptomatic patients, and the calcium score was available for only a few patients. Additionally, we do not have data about additional procedures such as surgical or catheter-based treatment of AF or left atrial appendage closure.

3. CONCLUSIONS

AF is an actor and an independent marker of poor prognosis in SAS patients. Furthermore, despite exhibiting a higher symptom burden, patients with AF are referred for AVR less frequently, even though they derive similar benefits from AVR as SR patients. Assessing the severity and functional impact of AF

in SAS patients is challenging and as such should be addressed in further prospective studies in order to aid clinical decision-making.

6.4. EXPERIMENTAL STUDY: "Ex Vivo" 18F-NaF Uptake, a Surrogate Marker of Calcific Activity in Aortic Valve Stenosis

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PRELIMINARY UNPUBLISHED DATA

1. INTRODUCTION

Aortic stenosis is a common condition associated with significant morbidity and mortality. Its pathophysiology involves chronic inflammatory response and prominent remodeling of the extracellular matrix, characterized by the development of fibrosis and—most notably—excessive calcification, which is the primary driver of its advancement [(250)]. Although all patients experience disease progression over time, the rate of progression at an individual level is difficult to predict [(80)]. Therefore, there is an unmet need for a tool to monitor disease activity effectively [(251)].

18F-sodium fluoride (18F-NaF), a bone-seeking PET/CT tracer, demonstrates potential in detecting active calcification and predicting progression. Unlike CT calcium scoring, which quantifies total calcification burden, 18F-NaF specifically identifies active regions. Studies link 18F-NaF uptake to calcification growth, hemodynamic valve deterioration, and an increased risk of clinical outcomes, such as cardiovascular events and/or the necessity for valve replacement [(13,60)]. In addition to metabolic imaging, high-resolution anatomical imaging via advanced CT scanners provides increasingly detailed insights into microtissue structures. In cases of aortic stenosis, the ability to detect microcalcifications (< 50 µm), which are associated with disease progression and occur prior to the formation of macrocalcifications (200-500 µm) detectable by conventional CT, has been made possible through these novel technologies applied to ex vivo specimens [(191)].

Given the potential complementarity of these imaging modalities and the promising clinical applications of the 18F-NaF tracer, we investigated its distribution on explanted aortic valves and its correlation with calcification density. We aimed to demonstrate its selectivity through epitope saturation (blocking). Additionally, we sought to visualize microcalcifications using high-resolution nano-CT imaging and to correlate their presence with 18F-NaF tracer uptake. Our objective was to demonstrate that NaF preferentially

binds in areas of microcalcification, with reduced binding in macrocalcification zones, thereby supporting its use in clinical studies assessing AS progression. We hypothesized a nonlinear relationship between tracer uptake and calcification burden, suggesting that signal intensity is not merely proportional to the total calcium deposit load but rather depends on the expansion of microcalcifications throughout the valve.

2. MATERIALS AND METHODS

SPECIMENS ACQUISITION AND PROCESSING

From May 2021 to September 2023, human aortic valves were collected from various sources. Moderate to severe stenotic aortic valves were obtained from patients undergoing aortic valve replacement at Cliniques Universitaires St-Luc. Each patient signed a consent form the day prior to their procedure to authorize sample collection. Additionally, aortic homografts were obtained from the European Homograft Bank. These valves were provided due to the presence of lipid or calcific deposits that rendered them unsuitable for clinical use. All specimens (**Figure 1**) were meticulously dried to remove microdroplets, then submerged in a liquid nitrogen bath and stored at -80°C to ensure optimal preservation.

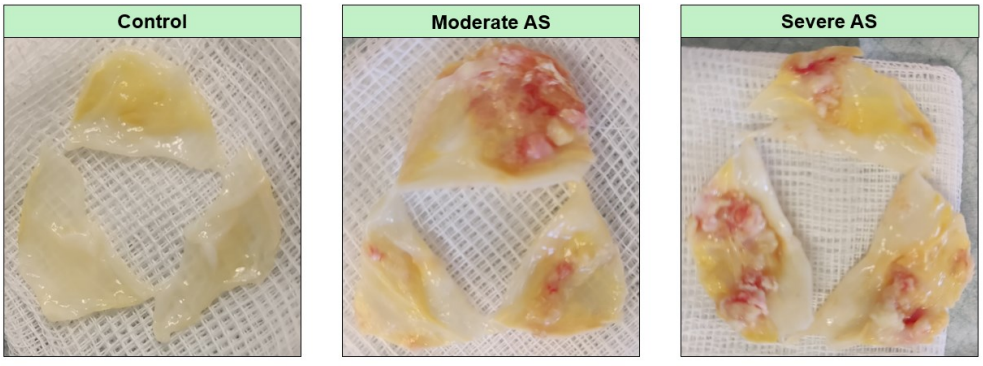

Figure 1: Example of aortic valves. Control valves were obtained from the

homograft bank, while stenotic calcific valves were collected in the operating room.

IMMUNOHISTOLOGY

A limited number of specimens were utilized for histological examination and immunostaining to identify inflammatory cells and proteins associated with ossification. Initially, the valves were fixed in a formaldehyde bath for 48 hours, followed by decalcification using a commercial solution (OSTEORAL R1 - RALA320715-1000). The duration of the decalcification process varied based on the degree of calcification, ranging from 24 to 72h. The specimens were subsequently embedded in paraffin and sectioned into slides for analysis. Immunostaining was conducted using primary antibodies targeting CD68, CD163, CD206, and Osteocalcin (**Figure 2**).

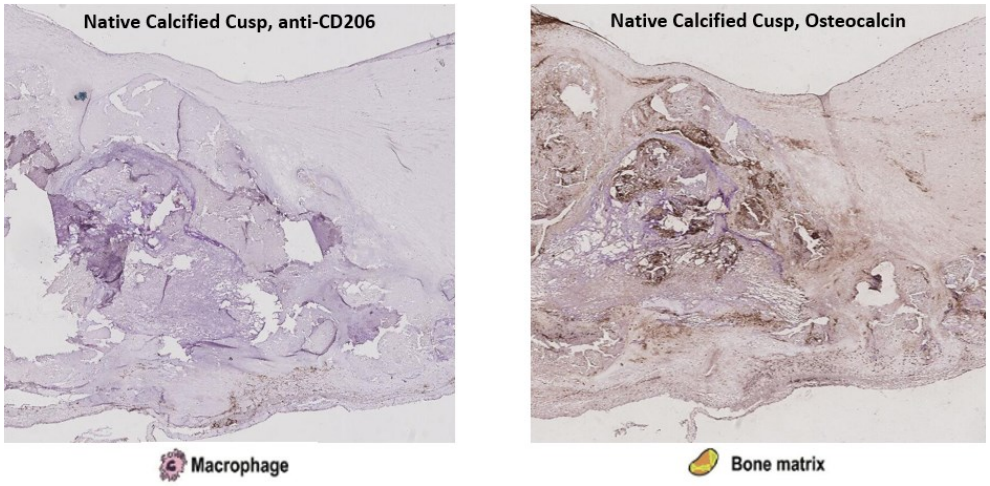

Figure 2: Immunohistochemistry images depicting macrophage (M2 subtype) staining on the left and osteocalcin staining on the right. Osteocalcin confirms the presence of bone tissue in our samples.

18F-NAF TRACER AND MULTIMODAL IMAGING

The ex-vivo imaging protocol is summarized in **Figure 3**. Specimens were initially thawed in a refrigerator and subsequently brought to room

temperature before being dried with compresses and weighed. Valves designated for blocking were incubated in an unlabeled NaF solution (2 g/100 ml) for a duration of 45 minutes. All samples were then immersed in an 18F-NaF solution (± 10 MBq in 50 ml) for an additional 45 minutes. This was followed by three 5-minute washes in PBS, with residual activity measured in the rinse water to ensure optimal wash-out, confirming that the activity measured by PET would originate from the tissues themselves. The cusps were then secured to a polystyrene board using surgical sutures and mounted onto a sample holder with benchmarks for optimal fusion of the PET and CT images. Three butterfly tubes filled with approximately 2 µCi of 18F-NaF and iodine were positioned in different planes to serve as 3D reference markers. The sample holder was then horizontally imaged using a small-animal PET scanner (Mosaic, Philips Medical Systems, The Netherlands), with a voxel size of 1 mm, for a 15-minute acquisition time. The specimens (still fixed within the sample holder and on the same bed) were subsequently transferred to a CT scan (CT Small Animal Imager, Bioscan, Inc.), with a voxel size of 220 µm, operating at 55 keV. After scanning, the polystyrene board was gradually refrozen to -80°C for preservation.

All samples were also imaged on Day 2 using the Phoenix Nanotom M (GE Measurement and Control Solutions, Germany) equipped with a 180 kV/15 W energy nanofocus X-ray tube and a diamond-coated tungsten target. Samples were once again thawed, dried, and mounted on a vertical sample holder with a calibration bead to normalize grayscale levels. The duration of each scan depended on the desired resolution, ranging from 5 to 50 microns (voxel size).

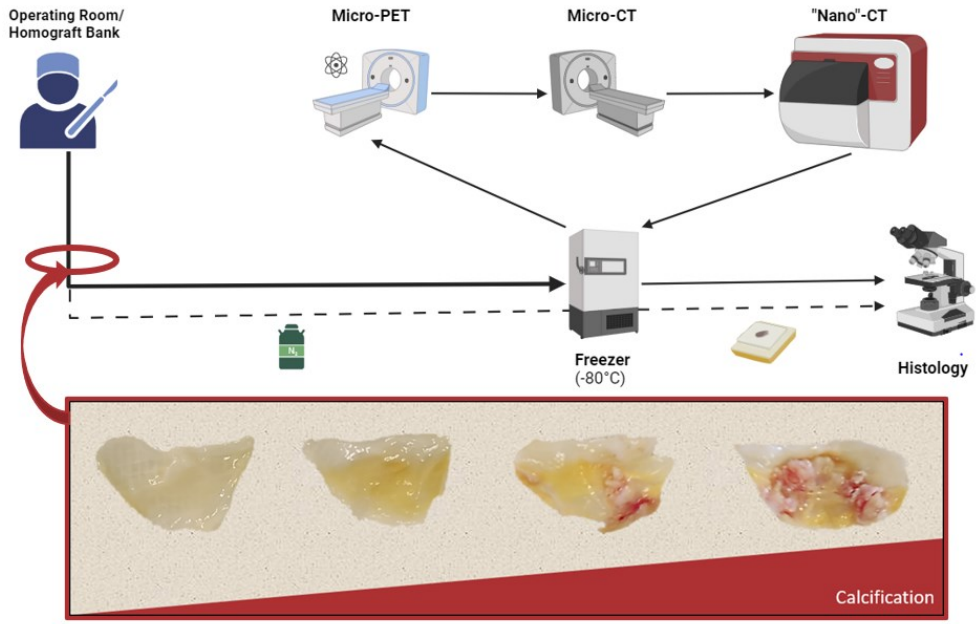

Figure 3: Overview of the sample workflow: from acquisition and storage in a -80°C freezer to multimodal imaging (PET, Micro- and Nano-CT) and histological analysis.

POST-PROCESSING: CO-REGISTRATION AND QUANTIFICATION

NanoCT images were reconstructed from raw data and normalized for grayscale levels utilizing an in-house MATLAB code [(191)]. Co-registration of the different imaging modalities was performed using MIM software (MIM Encore version 7.1.3, MIM Software Inc.), employing 3D markers and adhering to the sequence microCT-microPET followed by microCT-nanoCT, which resulted in fused tri-modal images (**Figure 4**). Given the significant discrepancies in spatial resolution among the imaging modalities, specific volumes of interest (VOI) sizes were established for each modality to ensure more reliable quantification of tracer uptake and calcification density. For microPET, the VOI diameter was determined to be twice the full width at half maximum (FWHM), resulting in a measurement of 6 mm, and total counts within the VOI were recorded. For microCT, a VOI diameter of 3 pixels

(0.75 mm) was employed to assess average density in Hounsfield units (HU). All data were processed and analyzed using RStudio 1.4.1106.

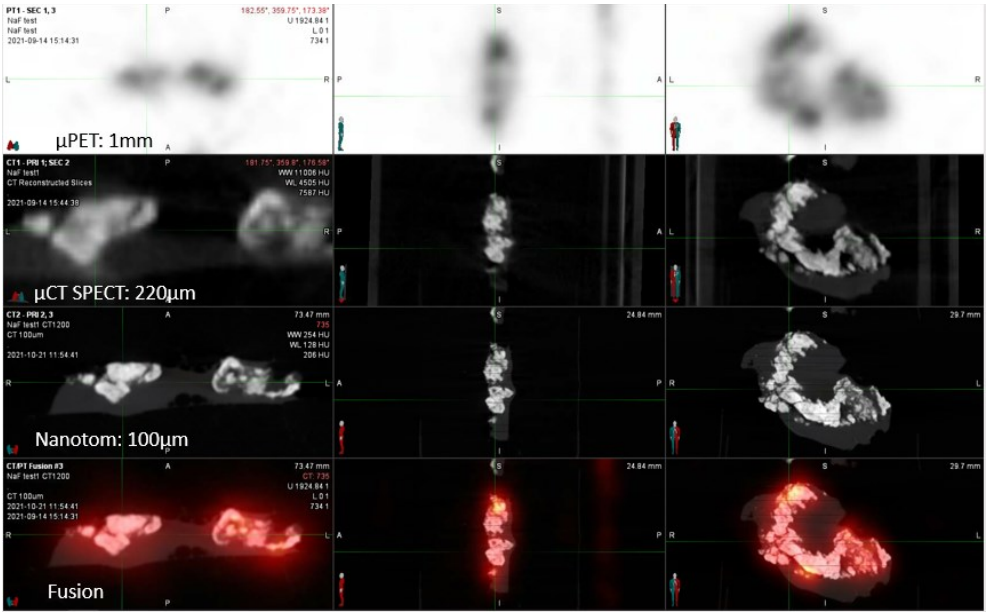

Figure 4: Example of multiple co-registrations of a calcified specimen performed using MIM software: First, the µPET signal is co-registered with the µCT image using 3D landmarks. Next, the µCT and nanoCT images are fused based on macrocalcification locations. These two co-registrations yield a final fused image that integrates all three imaging modalities. A distinct tracer uptake signal is evident on the final fused image, aligning precisely with calcifications across all three planes: transverse, sagittal, and frontal. The voxel size for each modality is specified.

3. RESULTS

A total of 16 homografts, 5 moderate aortic valves, and 11 severe aortic valves were collected over a 28-month period.

TRACER SELECTIVITY

Pre-saturating the interaction sites of 18F-NaF in the tissues by prior immersion in a 19F-NaF bath (blocking) resulted in the extinction of the PET signal in calcified areas (**Figure 5**). This observation was consistently reproduced across four different batches.

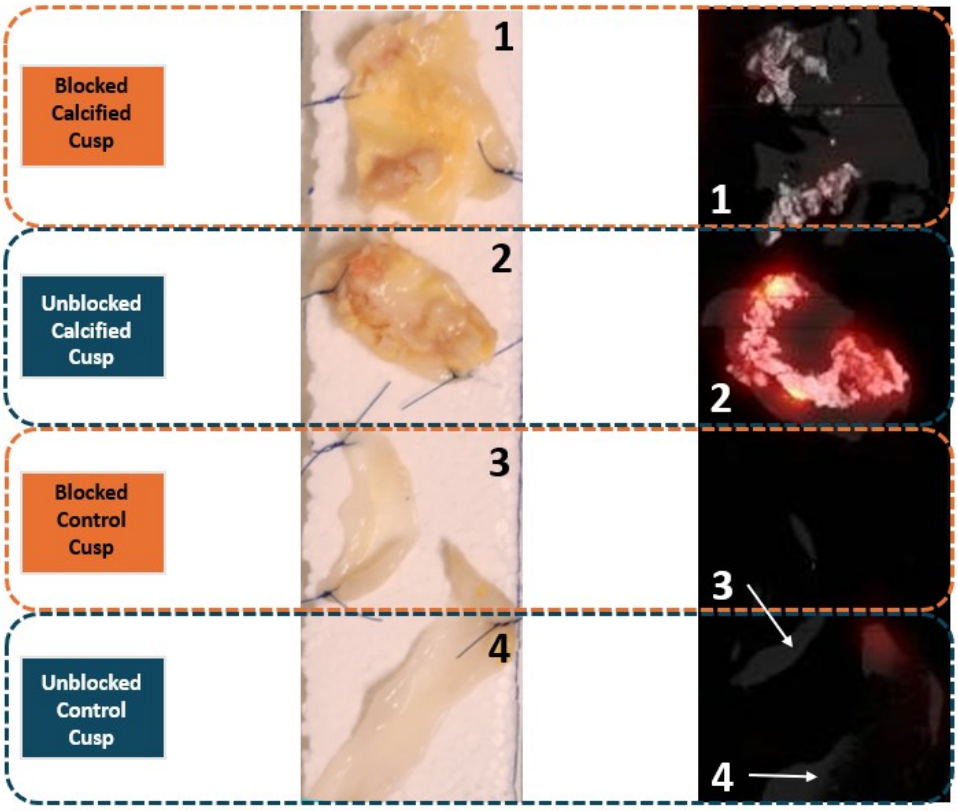

Figure 5: Examples of four valves imaged ex vivo by PET-CT. The top two valves are stenotic calcified valves, while the bottom two are control valves (homografts). Prior to incubation with 18F-NaF, two valves (calcified valve 1 and control valve 3) were saturated with unlabeled NaF tracer. The specificity of 18F-NaF labeling was clearly demonstrated, as no uptake was observed in the two valves previously blocked by unlabeled NaF. In contrast, a distinct tracer uptake signal was observed in the non-blocked valves

(calcified valve 2 and control valve 4). Notably, valve 4 shows signal uptake along its lateral edge, corresponding to an area of macroscopic thickening.

AREAS OF MICROCALCIFICATIONS

The high resolution of nanoCT enabled detailed visualization of the microscopic architecture of valvular calcifications. Anatomically, macrocalcifications and microcalcifications can theoretically be differentiated solely by size, with microcalcifications defined as being smaller than 50 microns. In heavily calcified specimens, distinguishing between macro- and microcalcifications is more challenging due to the extensive confluence of calcific clusters. Conversely, in less calcified specimens, we were able to identify regions of micro-attenuation, resembling fine sand, which correspond to areas of microcalcifications (**Figure 6**).

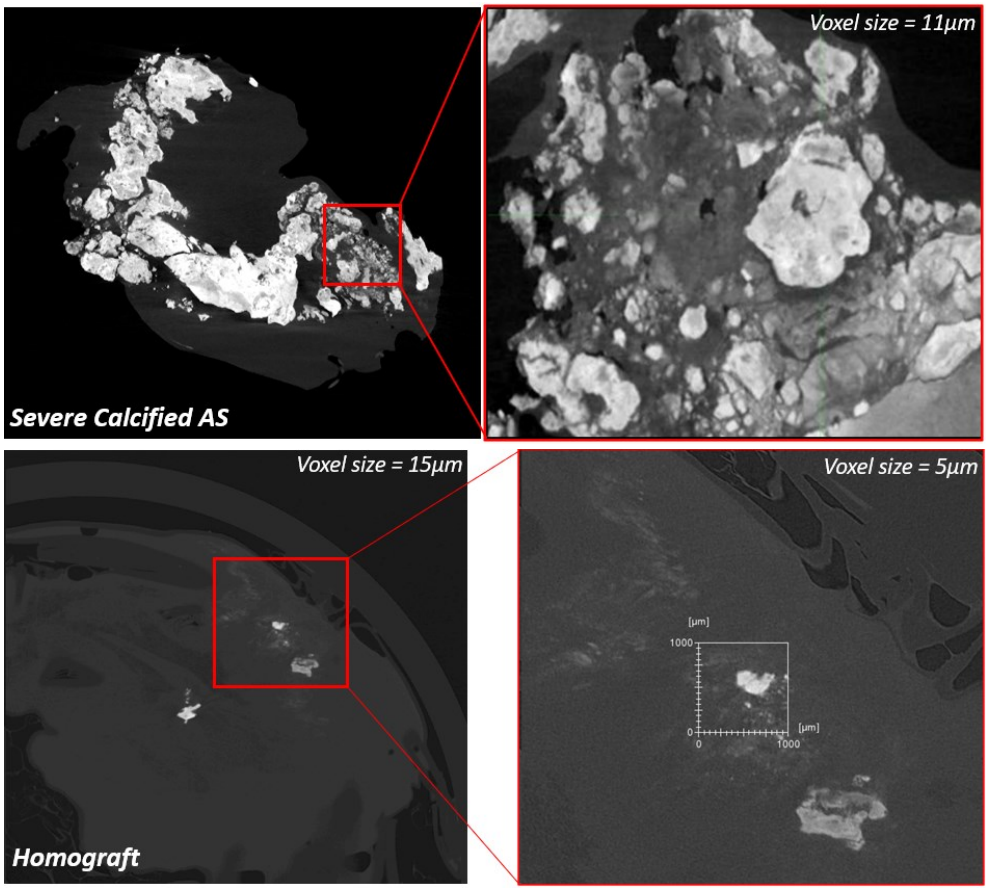

Figure 6: High-resolution CT images displaying the microstructure of calcific clusters within a severely calcified valve (top images) and a homograft (bottom images). In the bottom right image, a region of micro-attenuation resembling fine sand can be observed, corresponding to areas of microcalcifications. Interestingly, we also identified several calcified regions in the control valves with varying densities, demonstrating the presence of an "ongoing" calcification process.

The presence of these microcalcification areas, targeted by the 18F-NaF tracer, was also demonstrated via the detection of PET+/CT- mismatch regions in minimally diseased valves (homografts) (**Figure 7**).

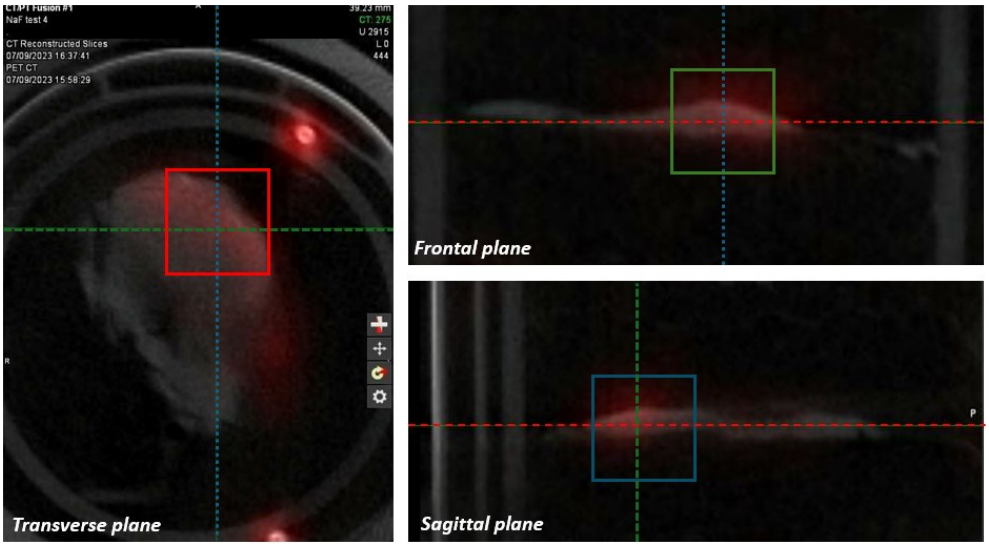

Figure 7: PET+/CT- mismatch region indicating the presence of a microcalcification area detected by the 18F-NaF tracer in a homograft.

SIGNAL QUANTIFICATION

A total of 44 volumes of interest (VOIs) were delineated on fused images across varying degrees of aortic stenosis severity, allowing for the measurement of total counts (on PET images) and mean density (on CT images) within the same area of interest. The relationship between these two parameters was plotted for each pair of measurements, revealing no linear correlation due to significant data dispersion. The adjusted R^2 for the linear regression model was 0.322, increasing to 0.543 for the quadratic model and 0.59 for the cubic model (**Figure 8**).

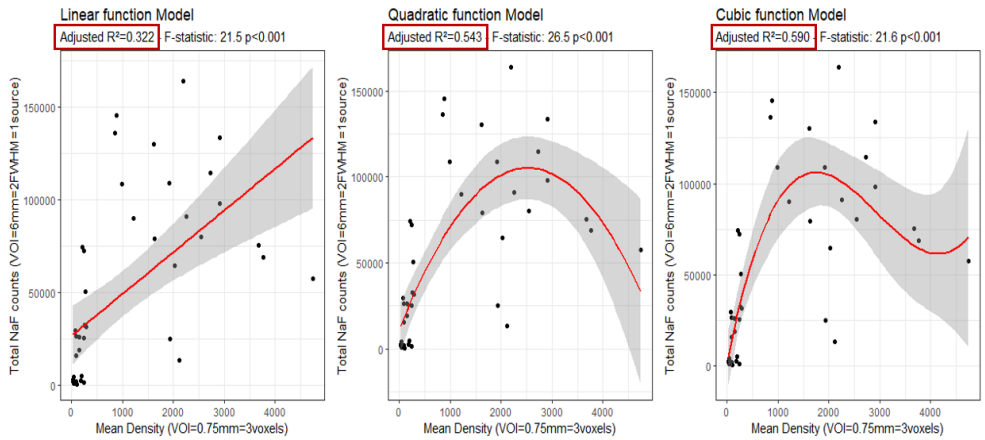

Figure 8: Multiple fitting models were applied using linear, quadratic, and cubic functions to evaluate the relationship between mean calcium density and the total PET counts of the 18F-NaF tracer.

The optimal predictive model for tracer uptake integrated a quadratic relationship with mean Hounsfield units (HU) and the tissue type where the VOIs were defined (soft tissue, calcification margins, or within a calcification). This model attained the highest adjusted R^2 of 0.678 and the most favorable goodness-of-fit parameters, including the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC) (**Table 1**). Notably, measurements taken specifically within calcified areas were not predictive of tracer uptake.

Table 1: Summary of best fitting models to predict 18F-NaF total uptake

	coef	P val	Adj R^2	AIC	BIC	Sum $Resid^2$
Model 1 = Third-degree polynomial						
Intercept	1987	0.804	0.589	1042	1051	3.9232e+10
Mean HU	139	<0.001				
Mean HU^2	-0.057	0.002				
Mean HU^3	0.000006	0.021				
Model 2 = Type of tissue						
Intercept	9591	0.157	0.618	1039	1048	3.6575e+10
Mean HU	2.3	0.758				
Lisière Ca	77260	<0001				
Calcification	71483	0.001				
Model 3 = Second-degree polynomial + type of tissue						
Intercept	3259	0.618	0.678	1032	1043	3.0028e+10
Mean HU	57.5	0.007				
Mean HU^2	-0.011	0.006				
Lisière Ca	54380	<0.001				
Calcification	17890	0.502				

P=0.0058

P=0.0013

BIC = Bayesian Information Criterion and AIC = Akaike Information Criterion.

The analysis of point dispersion based on the type of tissue where measurements were taken, combined with the presence of a PET signal, allows for several observations to be made (**Figure 9**). First, among the measurements performed on soft tissue without visible calcification on CT, certain areas exhibit uptake while others do not, despite falling within the same low-density range (red circle). The points with a signal likely correspond to areas of microcalcification, given the selectivity of the tracer. The second observation is that there are macrocalcifications with low activity, presenting weak signals (blue rectangle). Finally, the third observation involves calcification edges, where highly intense hotspots are detected (green rectangle), comparable in intensity to certain macrocalcifications.

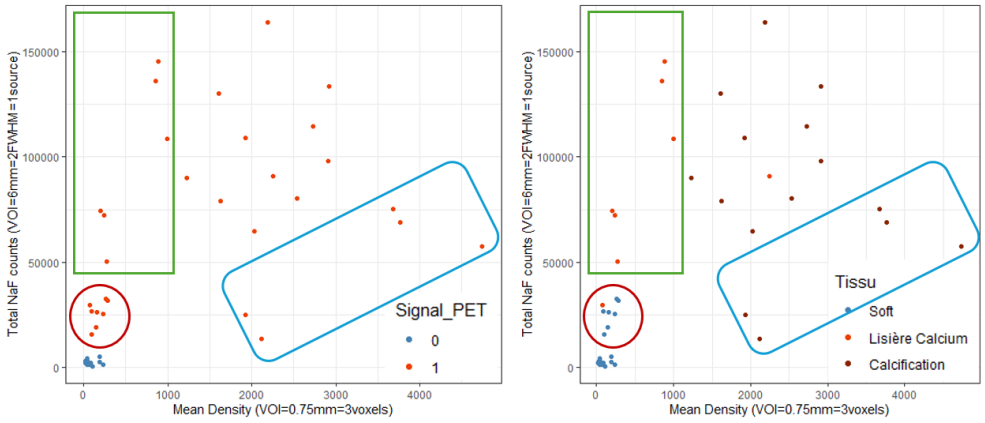

Figure 9: A scatterplot of total **18F-NaF** counts versus mean tissue density reveals three distinct patterns: hot soft tissue regions indicating microcalcifications (red circle), low-uptake macrocalcifications (blue rectangle), and highly active calcification edges with intense uptake (green rectangle).

4. DISCUSSION

This experimental study investigated the distribution of 18F-NaF PET/CT tracers on explanted aortic valves and the correlation with calcification density. The relevant findings were:

- This bone-seeking tracer can bind to its target in explanted valves using ex-vivo methodology.
- 18F-NaF exhibited a significant selectivity for calcific deposits, as pre-blocking of the tissues with unlabeled NaF completely inhibited further tissue tracer uptake.
- Areas of microcalcification were identified both directly through high-resolution CT imaging and indirectly by detecting mismatching PET+/CT- regions.

- Finally, a marked heterogeneity in tracer uptake was observed among valves, underscoring the nonlinear relationship between tracer uptake and calcium burden.

Molecular imaging is not routinely utilized in the management of aortic stenosis. However, there is a need for complementary investigative parameters to enhance the understanding and prediction of disease progression in patients. In this context, 18F-NaF is a promising marker, as numerous studies have demonstrated its ability to predict calcification score progression, hemodynamic valve deterioration, and the occurrence of clinical outcomes, as detailed in the introduction. Our findings resulted from an assessment of the tracer's ability to bind to microcalcifications, confirming its potential to detect the ongoing calcification process in valvular tissue. It also suggests that tracer uptake reflects more than just the extent of calcification, thereby providing incremental information beyond what is captured by the calcium score alone.

The ultimate goal is to develop pharmacological treatments capable of preventing or halting the progression of aortic stenosis. In this context, reliable monitoring tools are essential to assess treatment efficacy and guide patient follow-up. 18F-NaF PET imaging may emerge as a promising candidate for this purpose, and more broadly, metabolic imaging represents a compelling clinical endpoint in research studies, as it is more likely to reflect disease activity and treatment response over relatively short periods of time. However, availability and cost remain significantly higher compared to calcium scoring, and the technique is associated with greater radiation exposure. To date, no standardization of SUV or TBR values has been established for risk stratification, and it must be acknowledged that the added value of metabolic imaging in advanced stages of disease is modest, and virtually negligible in cases of severe stenosis.

In the context of this work, several limitations should be noted. First, co-registration was performed manually using 3D markers. Additionally,

significant plastic deformations were observed, preventing satisfactory co-registration in certain cases (**Figure 10**).

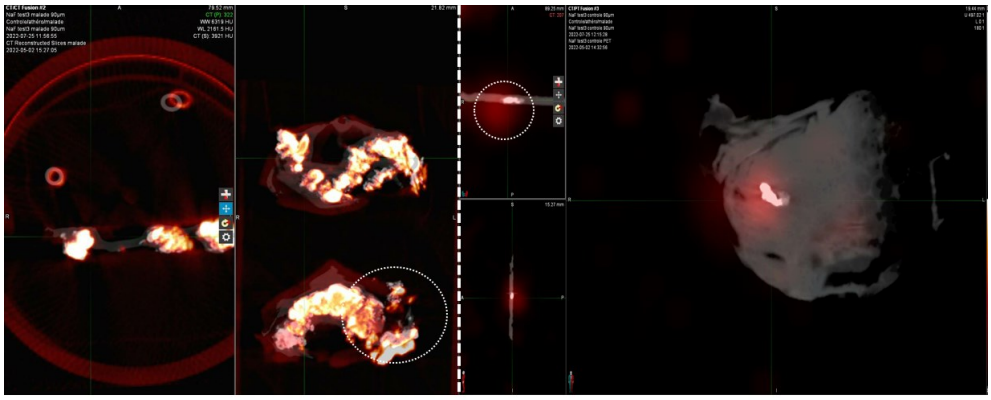

Figure 10: Example of plastic deformation hindering satisfactory co-registration.

Regarding quantification, several points need to be addressed. The lack of calibration for the equipment used introduced systematic errors, rendering it impossible to analyze raw measurement values directly. A conversion factor for photon attenuation, based on an assumed linear relationship, was calculated using other elements; however, it did not permit extrapolation of density values. Another major challenge was the significant discrepancy in resolution between imaging modalities, primarily constrained by the spatial resolution of the microPET imaging (1 mm voxel size), largely due to the inherent positron range of the 18-F radionuclide, among other factors. To minimize the partial volume effect, manually traced regions of interest were separated by a minimum distance of twice the FWHM. The resulting minimum distance of 6 mm substantially reduced the number of VOIs that could be included (**Figure 11**). Furthermore, VOIs of varying sizes needed to be traced depending on the imaging modality, despite sharing the same center, to mitigate considerable averaging effects.

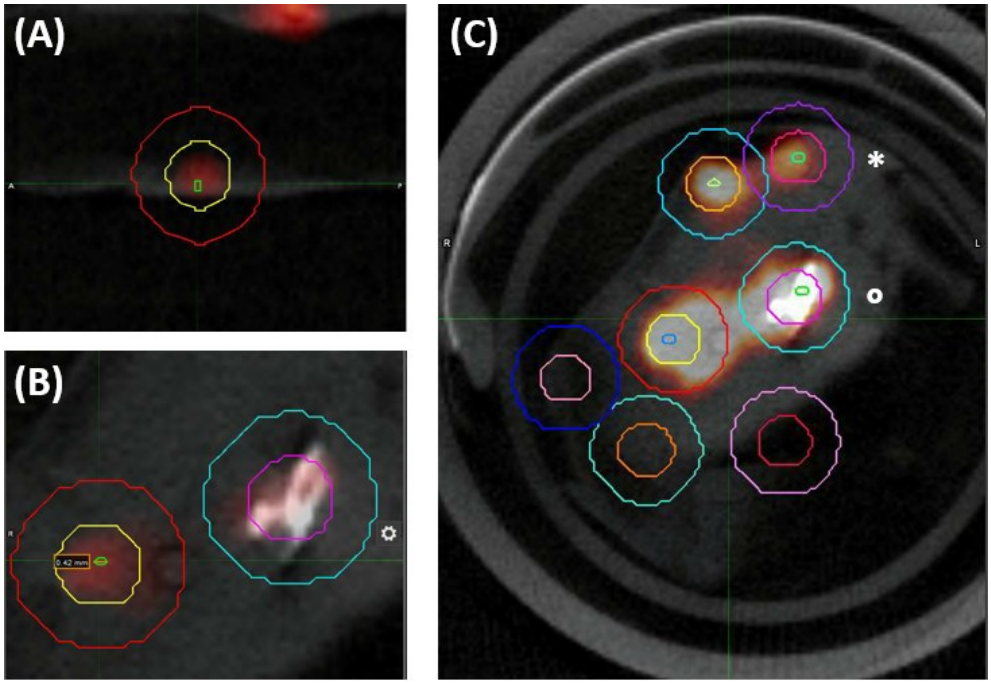

Figure 11: Example of manually traced volumes of interest (VOI) in valvular tissue. In some areas, three concentric circles are visible, corresponding, from the inside outward, to the VOI for CT imaging, the VOI at 1x full width half max (FWHM), and the VOI at 2xFWHM. Image (A) shows an isolated hot spot, with no particular issue for quantifying the tracer uptake. Image (B) reveals two hot spots that are separated without overlapping. Image (C) illustrates the challenge of defining multiple VOIs within the same sample: * indicates two VOIs at <2xFWHM while ° marks two sufficiently separated VOIs with signal loss between them.

As potential solutions to these limitations, the use of automated co-registration tools with plastic deformation correction capabilities is essential. In this regard, our team is focusing on utilizing the Avizo software (Thermo Fisher Scientific, Bordeaux, France) for our analyses. This tool will also facilitate segmentation based on grayscale values, allowing for improved delineation of tissue types and bypassing the need for machine calibration in order to work with Hounsfield units. Furthermore, enhanced

evaluation of tracer activity is advisable by normalizing the measurements to background noise using the TBR method.

Future directions for this project include assessing calcification activity using 18F-NaF through inter-valve comparisons across various echocardiographic severity stages and intra-valve analyses among different cusps within the same patient.

5. CONCLUSIONS

Ex vivo experiments on aortic valves using 18F-NaF PET-CT combined with high-resolution nano-CT imaging have demonstrated that 18F-fluoride specifically binds to and co-localizes with areas of both macro- and micro-calcifications, which are key drivers of disease progression. These properties make 18F-NaF a promising tracer for assessing disease activity and, consequently, for monitoring the effectiveness of future pharmacological therapies aimed at slowing or halting the progression of aortic stenosis.

Part 7. CONCLUSIONS AND PERSPECTIVES

7.1. Summary of the thesis findings

7.1.1. Understanding the prognosis of aortic stenosis

In terms of the prognosis of AS, the present work explored three main areas:

7.1.1.1. **What is the exact prognosis of discordant low gradient severe aortic stenosis (DLG-SAS), and what is its exact place in the disease continuum?**

Addressing this issue is crucial, as such discrepancies (AVA < 1 cm^2 with lower-than-expected transvalvular gradients and preserved LV function) are commonly observed in clinical practice, as well as since true severity assessment in AS is a vital step in the clinical decision-making process. Accounting for the prognostic impact of various confounding factors was a key focus in this work, given the highly heterogeneous nature of our population. We demonstrated that the prognosis of DLG-SAS patients was intermediate compared to that of MAS and HGSAS patients. We also showed that at comparable MG (DLG-SAS vs. MAS), the prognosis of patients depended on valve area: the smaller the valve area, the worse the prognosis. Conversely, at comparable AVAi (HG-SAG vs. DLG-SAS), the prognosis of patients depended on pressure gradient: the higher the gradient, the worse the prognosis. These findings strongly support existing evidence suggesting a less adverse prognosis in DLG-SAS compared to HG-SAS (**Figure 35**, point 1). The significant heterogeneity of the DLG-SAS population has always made prognostic comparisons with HG-SAS very difficult due to multiple confounding variables, including comorbidities and structural or functional myocardial parameters. This heterogeneity significantly contributes to the conflicting prognostic results reported in the literature. Our study helped clarify the real prognostic impact of these different valvular severity entities. Our work also highlighted a range of variables that substantially impact

prognosis and should be systematically considered in clinical assessments of patients with AS.

7.1.1.2. **What is the exact impact of waiting for Class-I triggers before operating on patients with high-gradient aortic stenosis?**

Current guidelines for referring SAS patients for AVR are primarily based on the presence of symptoms or left ventricular dysfunction. While studies suggest that asymptomatic patients with preserved ejection fraction have survival rates comparable to the age- and sex-matched general population for several years[10,209], growing evidence indicates that these triggers often reflect a late stage of the disease, potentially exposing patients to irreversible myocardial damage and worse outcomes. Consequently, determining the optimal timing for intervention in asymptomatic SAS remains an active area of investigation. In our study, we assessed the long-term postoperative survival of HG-SAS patients from a large multicenter cohort according to the presence of Class I triggers at the time of intervention. We demonstrated that the presence of Class I triggers (i.e., symptoms or LVEF <50%) at the time of intervention in HG-SAS patients was associated with increased long-term postoperative mortality risk compared with those without any triggers (approximately 45% greater risk of postoperative death at 10 years). Our data also indicated that an LVEF <60% at the time of AVR was associated with a 10-year postoperative survival penalty, while performing AVR in asymptomatic HG-SAS patients with an LVEF >60% resulted in outcomes similar to the general population. In our registry, symptomatic patients or those with LVEF <60% who underwent AVR experienced an 8.3- and 11.4-month survival loss, respectively, compared with those operated on without symptoms and with an LVEF >60% (after 10 years). Our findings question the necessity of maintaining an LVEF threshold in the guidelines and advocate for an “early AVR strategy” in asymptomatic patients with HG-SAS (**Figure 35**, point 2). Well-designed RCTs are needed to confirm these data.

7.1.1.3. **What is the prognostic impact of atrial fibrillation in patients with aortic stenosis and what is its impact on the decision to operate on patients with severe aortic stenosis?**

It remains uncertain whether AF, which is a highly prevalent condition in SAS, acts as a direct causal factor contributing to adverse outcomes, or whether it merely serves as a marker of advanced cardiac disease. Specifically, AF is not currently recognized as a guideline-based trigger for aortic valve replacement—its presence can affect the assessment of AS severity and can influence the clinical decision-making process regarding AVR eligibility.

Utilizing a large cohort of patients, we demonstrated that in the presence of severe AS, patients with AF have consistently worse survival outcomes than SR-patients, regardless of whether they underwent AVR (**Figure 35**, point 3). Furthermore, while both AF and SR patients benefit from AVR to a similar extent, AVR is systematically performed less frequently in AF patients than in SR patients. Even after adjusting for other clinical and imaging factors influencing referral, including symptoms and transvalvular gradients, AF remains an independent predictor of reduced referral to AVR. Assessing the severity and functional impact of AF in SAS-patients is challenging and should be addressed in further prospective studies in order to assist with clinical decision-making. From our point of view, the existence of AF in the presence of SAS should prompt consideration of AVR and should not be used as a rationale to delay surgery.

7.1.2. Contributions to the metabolic signature in aortic stenosis

Despite increasingly advanced knowledge of the pathophysiology of aortic stenosis, as of yet no pharmacological treatment has successfully slowed the progression of the disease. As such, a deeper understanding of the underlying metabolic processes remains crucial, not only for developing future therapies, but also for creating tools to monitor their effectiveness

over time. We therefore aimed to explore the capabilities of metabolic imaging in AS by conducting an ex-vivo experimental study using a bone-specific PET tracer, seeking to investigate the valvular calcification activity in relationship with micro- and macro-calcifications. We further aimed to demonstrate the presence of microcalcifications through the use of a very-high resolution nano-CT.

We ultimately demonstrated that this bone-seeking tracer (18F-NaF) can bind to its target in explanted valves using a reproducible methodology. Furthermore, we revealed that the 18F-NaF tracer is highly selective for calcified deposits, as prior blocking of tissue with unlabeled-NaF completely inhibits any subsequent tracer uptake. For the first time, we could identify the presence of areas of microcalcification in aortic valvular tissue, and could also detect several valvular PET+/CT- mismatch regions, thereby confirming the 18F-NaF tracer's ability to bind to “ongoing calcification process” (**Figure 35**, point 4). We are thus convinced that this tracer is promising for monitoring future potential pharmacological therapies designed to slow or halt the progression of early-stage aortic stenosis.

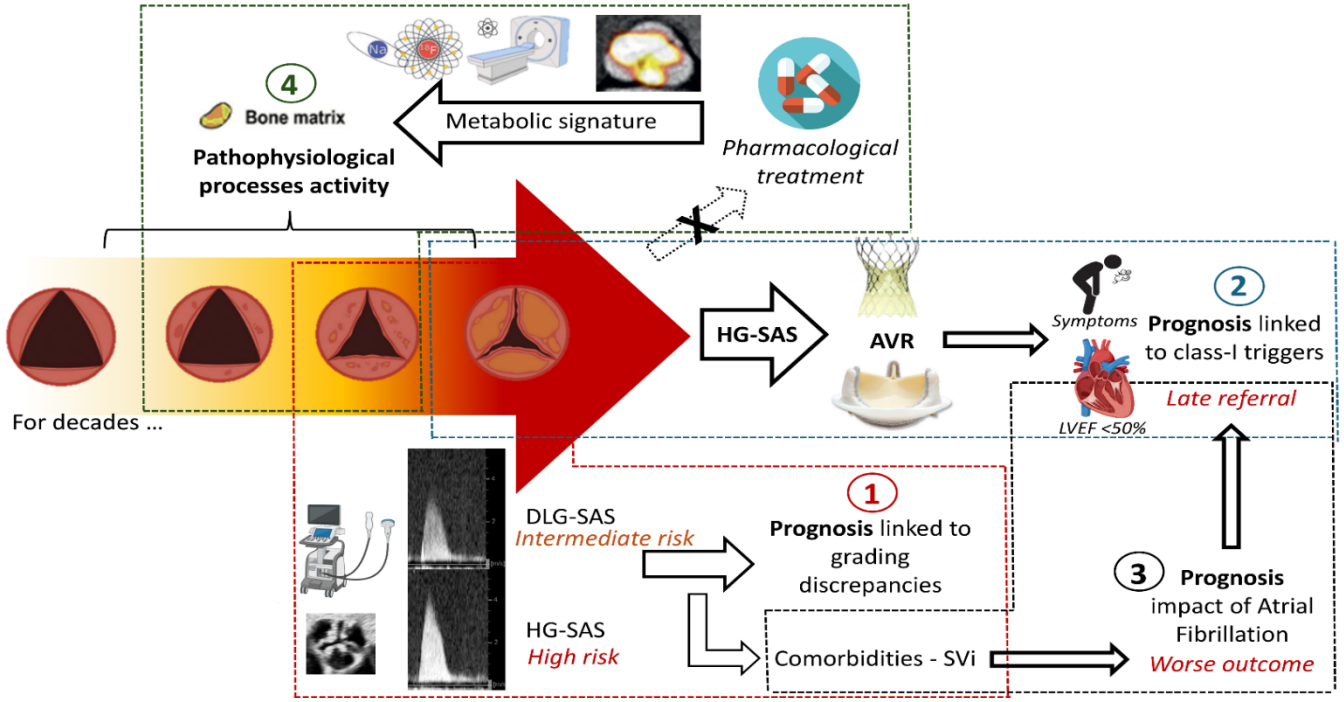

Figure 35: ***Graphical abstract.*** *Summary of the main research themes explored in this thesis: (1) low-gradient discordant aortic stenosis represents an intermediate stage with high comorbidity burden and adverse prognosis; (2) class I indications for aortic valve replacement are linked to reduced long-term survival, suggesting late-stage disease at referral; (3) atrial fibrillation is a common comorbidity, associated with poorer outcomes and late referral; and (4) 18F-NaF PET uptake co-localizes with active calcification, emerging as a marker of disease activity, progression risk, and a potential tool for therapeutic monitoring.*

7.2. Critical appraisal

7.2.1 **Significance of grading discrepancies**

The diagnosis of DLG-SAS is based on echocardiography and is influenced by measurement errors, approximations in the formulas used, parameter threshold values in the definitions, and flow conditions. Additionally, there is a higher prevalence of comorbidities in the DLG-SAS population. All of these factors contribute to significant heterogeneity among patients falling under this definition.

In our study, we accounted for as many comorbidities as possible, alongside echocardiographic parameters that are independently associated with patient prognosis. From a methodological perspective, we employed pseudo-randomization techniques to enhance the comparability of our groups. However, it is crucial to acknowledge that these methods have several limitations. For instance, inverse probability weighting (IPW) has the benefit of retaining all patients by assigning them a weight inversely proportional to their probability of belonging to their respective group based on selected characteristics. This approach increases the weight of the most extreme variants, thereby raising the standard error of value dispersion and normalizing intergroup differences. Conversely, propensity score matching selects comparable patient profiles but leads to significant patient exclusion. Furthermore, the quality of matching diminishes as the number of pairs formed increases. While these statistical methods are useful, they remain somewhat artificial, particularly regarding patient profile selection, and cannot replace randomization at inclusion. True randomization relies on chance to balance both known and unknown factors, whereas pseudo-randomization can only adjust for known variables. Given these limitations, it must be recognized that determining the true prognostic impact of severity discordances from a solely valvular perspective is theoretically interesting but may not fully reflect clinical reality. Aortic stenosis is not merely a valvular disorder but rather a complex disease intertwined with a

broader clinical picture, frequently accompanied by numerous comorbidities that cannot be disregarded in practice. This assertion is essential for understanding the inconsistencies reported in the literature.

Stroke volume index was an integral component of our adjustment models, treated as a continuous variable rather than a categorical one. This approach is essential, as the definition of low-flow status is debated due to its low sensitivity; approximately 30% of healthy individuals may physiologically present with an SVi < 35 ml/m². Nonetheless, most studies concur that reduced flow is associated with a poorer prognosis. Consequently, we sub-stratified our DLG-SAS population categorically into normal-flow (NF) and low-flow (LF) groups. Although we observed a trend toward curve separation, this did not reach statistical significance. Once again, the relationship between comorbidities and low flow—whether causal or associative—can obscure or amplify the effect of SVi on prognosis, depending on the adjustment parameters employed. What appears far more crucial is understanding the underlying cause of the low-flow status. A physiological low flow due to constitutionally small left side cavities does not carry the same prognostic implications as a low flow state caused by restrictive cardiomyopathy combined with mitral regurgitation and atrial fibrillation. Cardiac amyloidosis is another possible scenario, as it commonly coexists with SAS, especially in the setting of a low-flow state, and further worsens the prognosis of patients with LFLG.

Treating DLG-SAS or even MAS patients is likely to improve patient prognosis due to the progressive nature of the disease: all such patients will inevitably progress to a more severe form of the disease, resulting in worse outcomes. This approach could be justified if valve substitutes possessed an unlimited lifespan and never became infected; however, current evidence indicates that this is not the case. Consequently, the patients who would benefit the most from treatment (considering the risk-benefit balance) are undoubtedly those with HG-SAS. Transcatheter AVR is increasingly being proposed and is becoming the standard treatment, even for low-surgical-risk patients.

Nevertheless, this treatment is associated with significant risks and high costs. Therefore, it is essential to refrain from offering potentially futile treatment to patients who can be safely followed up and monitored clinically, especially in case of frailty, advanced age, and multiple comorbidities. Our data support this perspective. These patients must be meticulously selected by weighing the treatment against the natural prognosis of the disease. Randomized prospective studies are needed to clarify the benefit of AVR for patients with DLG-SAS.

7.2.2 **Late referral to AVR associated with guideline Class I triggers**

Waiting for symptoms or LV dysfunction to occur or develop before operating on HG-SAS patients is associated with reduced long-term postoperative survival. These conclusions align with a growing body of evidence supporting an earlier AVR strategy in this population [215,216,218].

Despite these observations, the decision-making process for AVR referral outlined in international guidelines remains primarily symptom-based. Specifically, this criterion ranks highly in the decision tree, introducing an element of subjectivity early in patient management. A set of Class IIa recommendations is subsequently included, allowing for the identification of high-risk patients who may benefit from AVR, even in the absence of reported symptoms. However, not all patients fit into such categories.

While studies generally agree that asymptomatic patients with SAS have a favorable prognosis comparable to the general population, predicting the timing of any deterioration in their condition remains inherently challenging, risking late referral with potential prognostic consequences. Our findings align with previous research indicating that when severe symptoms develop, it is often too late to restore normal life expectancy [8,154]. However, patients with mild symptoms (NYHA Class 2) may still derive significant benefit from AVR, with survival rates comparable to those of the general population. Consistent with the aforementioned studies, we observed no difference in postoperative survival between patients in NYHA Classes 1 and 2 with

preserved LVEF. Furthermore, if the presence of mild symptoms does not affect prognosis, this would underscore the existence of a narrow window for timely intervention, which could be missed depending on the frequency and quality of follow-up. Conversely, if a prognostic difference is present in patients with mild symptoms, this further highlights the necessity of moving beyond subjective assessments of the functional impact of AS.

To address these concerns, exercise testing and natriuretic peptide measurement have been proposed as additional screening tests. However, these parameters come with their own limitations. For example, exercise testing in particular has exhibited a limited capacity to predict the rapid onset of symptoms. This was strikingly demonstrated in the recent Early TAVR RCT [218], where 26.2% of patients in the conservative management arm with a negative exercise test at baseline required AVR due to symptom development within six months, increasing to 47.2% after one year. Natriuretic peptides, on the other hand, may either overestimate or underestimate the cardiac impact of SAS, making it essential to consider conditions that could influence their measurement [252] before any decision-making.

The survival penalty associated with even a modest LVEF reduction is not surprising, given its late decline in the disease's pathophysiology. Nevertheless, these findings raise the question of whether a specific LVEF cutoff should be established to guide intervention, especially considering the proportional increase in mortality risk with decreasing LVEF. On the other hand, subtle and early markers of LV dysfunction could offer a better means for making therapeutic decisions. Ventricular maladaptive hypertrophy, which precedes systolic dysfunction, could emerge as a novel early prognostic marker, assessable through MRI (T1 mapping [120], ECV [115,119,253], LGE [115-118,253,254]) or by measuring GLS [100,194,253].

Proposing AVR to all asymptomatic HG-SAS patients before the onset of symptoms or LV dysfunction remains a contentious issue. Changing current recommendations to adopt such a strategy would require robust evidence

from well-designed RCTs, which are not yet sufficient to support generalization in favor of early AVR. This approach continues to be actively debated among experts, who weigh its potential advantages and limitations.

On the **pro side**, arguments in favor of the early intervention include the significant limitations of watchful waiting strategy, such as suboptimal follow-up in real-world settings, challenges in assessing symptoms, the risk of sudden death, and the increased morbidity and mortality associated with late referrals. Additional concerns include the risk of irreversible consequences, particularly myocardial fibrosis, but also left atrial or mitral valve damage, pulmonary hypertension, or right heart failure, all of which are associated with poorer outcomes [(208)]. While not all of these features are direct consequences of AS, their occurrence would likely be less common with earlier intervention. Moreover, advancements in surgical and percutaneous techniques in valve replacement have reduced procedural risk, altering the risk-benefit ratio.

On the **contra side**, arguments against early AVR focus on the risks associated with the procedure, including interventional mortality, valve thrombosis or thromboembolism, bleeding, prosthetic valve endocarditis, paravalvular regurgitation, the need for permanent pacemaker placement, and structural valve deterioration. Early intervention with biological valves also suggests the necessity of earlier re-intervention, raising concerns about long-term durability. Furthermore, potentially irreversible cardiac damage could be identified early through careful follow-up and advanced imaging, presenting an alternative to early surgery. Lastly, the limited generalizability of RCT results, which are often derived from highly selected populations, remains a significant challenge for endorsing early intervention as a universal strategy.

7.2.3 **Atrial fibrillation in aortic stenosis: a dangerous connection**

The onset of AF during the course of AS significantly impacts and influences patient prognosis. However, we currently lack tools reliable enough to

accurately predict its occurrence. Left atrial dilation could serve as an early marker of atrial disease from which AF originates, as well as a warning signal. Indeed, recent studies suggest that a left atrial volume >50 ml/m² is associated with increased mortality, particularly when accompanied by arrhythmia [11,255]. Another factor that likely contributes to poorer outcomes in AF patients is the underutilization of ablation therapy in this specific population [256]. Beyond valvular management, it would be worthwhile to investigate the impact of early ablation in AS patients, similar to those strategies employed in regards to patients suffering from heart failure [257].

AF also reduces forward flow, thereby affecting Doppler-measured gradients, contributing to symptoms, and being more frequently associated with comorbidities. These factors are among the primary reasons for the under-referral of AF patients for AVR, despite evidence demonstrating that they benefit to the same extent as patients in sinus rhythm. The utilization of non-flow-dependent imaging modalities to assess AS severity should help mitigate the under-referral in this specific population.

More broadly, the case of atrial fibrillation in aortic stenosis once again underscores the delayed nature of certain management strategies, which arise from the definitions currently utilized in clinical guidelines. This reinforces the argument for evolving recommendations toward earlier valve replacement strategies, particularly if advancements continue in the direction of more durable valve substitutes and reduced implantation-related complications.

7.3. Perspectives in Aortic Stenosis

7.3.1. Prognosis: How can we further improve severity grading?

The current definitions of severe AS represent a significant source of discordance, affecting up to 30% of cases, and warrant reconsideration. As mentioned above, there is frequent misuse of the terms EOA, GOA, and Gorlin area, as if they were interchangeable, sharing identical severity thresholds, despite reflecting different physical phenomena. Defining specific cutoff values for each parameter could improve diagnostic accuracy. Nevertheless, Doppler-derived EOA measurement remains the most widely used technique, for which there are two potential approaches: lowering the AVA cutoff to 0.8 cm^2 to align with a mean gradient of 40 mmHg or lowering the gradient cutoff to 30 mmHg to correspond to an AVA of 1 cm^2. In the context of earlier intervention, the latter option may provide greater benefit to patients, considering the growing body of literature on the detrimental impact of moderate aortic stenosis. However, merely adjusting these cutoffs could introduce new discordances. Factors such as sex, flow status, and body surface area significantly influence Doppler-derived parameters, and the notion of a universal threshold is likely an oversimplification of a much more complex issue.

In this regard, incorporating the broader clinical context of the patient, such as myocardial staging, alongside valvular assessment, appears to be a more effective approach. For example, a patient with moderate to severe AS, significant left atrial dilation, atrial fibrillation, and elevated pulmonary pressures is likely to experience higher mortality than a patient presenting a mean gradient of 40 mmHg albeit without evidence of maladaptive myocardial remodeling. Adaptive mechanisms in response to increased afterload are likely to vary among patients, meaning that for the same degree of valvular stenosis severity, the resulting adverse effects can differ significantly. Additionally, the presence of overlapping conditions with phenotypes similar to aortic stenosis, such as HFpEF and cardiac amyloidosis,

is often underdiagnosed. This contributes to prognostic discrepancies and further reinforces the significant heterogeneity observed among patients. All these considerations underscore the importance of a comprehensive evaluation beyond “valvular status” alone.

Another significant challenge to the current strategy is its reliance on flow-dependent parameters. While low-flow status is a known marker of poor prognosis, its current definition lacks precision, as it encompasses a substantial proportion of healthy individuals (approximately 30%) who naturally exhibit reduced antegrade flow due to anatomical reasons. Refining the flow cutoff is therefore essential. An alternative to measuring flow, with all its associated interpretative challenges, would be to perform systematic cardiac CT scans in all cases of severity discordance. Although this approach is already supported by guideline recommendations for borderline cases, its implementation remains limited in daily practice, largely due to local habits and the availability of CT scanners. Nevertheless, the widespread use of calcium scoring combined with contrast-enhanced imaging to assess the presence of valvular fibrosis could significantly enhance the accuracy of patient evaluations. This approach could facilitate more precise reclassification of patients, thereby reducing diagnostic uncertainty and improving risk stratification. In the future, following the example of coronary FFR-CT algorithms, the development of hemodynamic measurements derived from CT or MRI could prove beneficial in certain patients for whom echocardiography is inconclusive.

7.3.2. Prognosis: How early should valve replacement be recommended?

The available body of evidence supports an earlier interventional strategy for patients with HG-SAS. Early intervention could prevent irreversible myocardial damage and enable patients to better withstand hemodynamic challenges, such as in the event of sepsis, hypovolemia, or other stressors.

However, replacing the valve in all HG-SAS patients upon diagnosis raises several important questions.

The first challenge is procedural risk; however, this has been significantly mitigated in recent years due to advances in percutaneous and surgical techniques. Moreover, operating on patients earlier in the disease course may potentially lower operative risk compared to a delayed approach, wherein comorbidities and hemodynamic compromise are more advanced. Other concerns persist, such as paravalvular leaks in TAVI procedures. Nonetheless, the development of next-generation prostheses with supra-annular sealing skirts has effectively minimized this complication. Another critical issue is the necessity for permanent pacemaker implantation, which carries long-term risks, including infection and deleterious ventricular mechanical activation. Physiological pacing techniques, such as left bundle branch pacing, present a promising alternative by reducing the risk of pacing-induced cardiomyopathy in many cases. Lastly, the risk of premature structural valve deterioration remains a pertinent concern, with approximately 30% of bioprosthetic valves exhibiting signs of degeneration within 10 years [(258)]. The durability of valve substitutes is a critical consideration and should be evaluated and weighed against the patient's expected remaining life expectancy.

In patients aged 75 years or older, an early valve replacement strategy appears appropriate given the challenges in symptom assessment, the increased likelihood of developing conditions that elevate procedural risk, and the alignment between the lifespan of the valve substitute and the patient's expected life expectancy. Such cases would likely benefit from this preemptive approach.

For younger patients whose life expectancy exceeds that of the valve substitute, the situation becomes more complex. These patients are generally more active, which facilitates symptom evaluation through discussion or exercise testing, and their surgical risk tends to remain lower

over time, as they are theoretically less likely to develop an intercurrent condition. These arguments may support proactive surveillance with close follow-up rather than earlier intervention. Additionally, the presence of a bicuspid aortic valve, with or without associated aortopathy, must also be considered, as it can significantly affect surgical risk and long-term management. The major concern in this population is the likelihood of requiring a second or even third valve replacement during their lifetime. Unfortunately, the risk of reintervention has not been thoroughly evaluated in current studies, as such assessments would necessitate follow-up periods exceeding 10 to 20 years. Postponing intervention until class I criteria are met is unlikely to lessen the need for a second procedure and may instead increase the risk of adverse outcomes for the patient.

Midterm outcomes for major cardiovascular events appear comparable between percutaneous and surgical AVR approaches, though a recent meta-analysis revealed a time-varying effect of TAVR versus SAVR at five years [(259)]. This study suggests that the early advantage of TAVI may diminish or even reverse over time, thus favoring surgery. Factors such as prosthesis durability, paravalvular leaks, along with the higher incidence of pacemaker implantation have been considered as potential contributors to these outcomes. However, both strategies are currently regarded as equivalent in terms of their effectiveness. Consequently, when considering a 20+ year timeframe, a key question emerges: which initial intervention—TAVI or SAVR—provides the best strategy and offers the most potential to minimize long-term complications and risks associated with reintervention? For patients under 75 years of age with low surgical risk, conventional surgery remains the recommended first-line approach in our countries [(5)]. To avoid a second sternotomy and reduce procedural risk, a valve-in-valve (ViV) strategy is likely to be recommended, considering that the patient will be older when the first valve substitute deteriorates. However, given that TAVI provides a larger AVA compared to the same-size SAVR, particularly in patients with small native aortic annuli [(260,261)], and that ViV in a degenerated TAVI is associated with lower residual gradients than ViV in a degenerated

surgical bioprosthesis [262], TAVI might be an appealing first-choice option in younger patients. This is especially relevant when considering longer survival times and the potential need for a future valve-in-valve-in-valve procedure to minimize the risk of patient-prosthesis mismatch (PPM). Indeed, severe PPM is associated with higher mortality, increased heart failure re-hospitalization, and accelerated bioprosthesis degeneration due to elevated valve stress and flow turbulence [263]. In patients with pre-existing PPM undergoing ViV implantation, supra-annular TAVI may be the preferred solution [264]. Adding complexity to this debate, another challenge associated with ViV is maintaining coronary access, which becomes significantly more difficult after a TAVI-in-TAVI procedure, particularly with supra-annular valve positioning [265,266]. Hopefully, new-generation prostheses with wider coronary mesh openings [266] and commissural alignment strategies [265] will potentially help reduce these risks.

Another drawback of initiating a life-long valve replacement strategy with TAVI is the potential requirement for subsequent surgical explantation. An analysis of TAVI explantation practices from the Society of Thoracic Surgeons (STS) database, encompassing 33 Michigan hospitals between 2012 and 2020, identified common indications such as procedure-related failure, paravalvular leak, the need for additional cardiac surgery, coronary obstruction, and endocarditis [267]. Surgical explantation of a TAVI remains an extremely challenging procedure, with high mortality rates (up to 20%) and morbidity rates [267-269], often necessitating aortic root repair or replacement due to prosthesis integration into the aortic wall (33% according to the STS database) [267]. Although the overall risk of TAVI explantation remains low, the increasing number of implanted TAVIs worldwide raises significant concern. This is particularly relevant in the United States, where TAVI is offered to patients starting at 65 years of age. Therefore, this risk should be carefully considered when selecting the initial interventional strategy. Finally, the evolving trend toward using TAVI as a first-line treatment, with surgical options reserved for unsuitable cases, introduces additional risks. Reduced surgical volumes may lead to a decline

in surgeons' experience and technical proficiency. These factors underscore the necessity for a lifetime management approach that prioritizes valve durability, future reinterventions, and personalized care.

Specific populations may benefit from earlier interventions and warrant special consideration, as they are likely to be included in future AVR guideline updates. Specifically, symptomatic moderate aortic stenosis is currently under investigation to determine whether these patients could benefit from early AVR, with current data suggesting increased mortality rates in cases where moderate AS is associated with LV dysfunction. Indeed, the elevated afterload on a weakened myocardium appears to be a high-risk condition. However, the UNLOAD TAVR trial failed to demonstrate the superiority of preemptive TAVI over medical treatment in reducing major cardiovascular events [(270)]. Further randomized controlled trials are needed to clarify these findings. Similarly, patients with at least moderate aortic regurgitation in conjunction with moderate AS appear to be at a comparable risk of adverse events to those with isolated severe AS [(271)]. Furthermore, heart failure with preserved ejection fraction or cardiac amyloidosis can also be associated with aortic stenosis, and are often underdiagnosed despite their significant impact on prognoses [(272)]. It is concerning that a considerable number of patients undergoing AVR are hospitalized for heart failure decompensation within one year following the intervention, even though the hemodynamic obstruction has been resolved. These patients frequently exhibit persistently elevated filling pressures, remain symptomatic, and have high H2FPEF scores [(273)]. In fact, the H2FPEF score appears to be a useful tool for predicting long-term adverse outcomes following TAVI [(273)], as it incorporates prognostic variables that are also relevant in aortic stenosis. However, the persistence of these factors following the resolution of the obstruction may indicate either a late intervention or the presence of an underlying associated condition requiring specific attention.

7.3.3. Prevention: Could metabolic imaging shape the future of preventive medicine?

While no drug therapy has yet proven effective in treating aortic stenosis, the ultimate goal remains the development of treatments that can slow or even halt disease progression. Evaluating the metabolic response to therapy offers a promising approach for optimizing patient management in secondary prevention. In this regard, PET imaging exhibits great promise due to its ability to target various ongoing metabolic processes. Specifically, in the context of AS, the 18F-NaF tracer offers potential applications in several scenarios. For native valves it could be used to monitor the anti-calcific activity of experimental pharmacological therapies and serve as a compelling clinical endpoint, as it is more likely to change over short periods than conventional echocardiographic parameters. For prosthetic valves, 18F-NaF imaging could also be applied in the context of tertiary prevention, offering a means to predict structural valve degeneration and tailor follow-up accordingly.

There is a great deal of research on emerging tracers that may aid clinicians in understanding and assessing complex pathophysiological mechanisms, that may ultimately lead to the prevention of valvular disease progression.

68Ga-FAPI: Gallium 68–labelled fibroblast-activation protein inhibitor (68Ga-FAPI) is a novel tracer that is currently a focus of interest among researchers in the field of myocardial infarction and aortic stenosis [(274)]. This tracer appears to be specific to “activated fibroblast,” and it may be of major interest in non-calcifying thickening regions in AS.

68Ga-Dotatate: This tracer targets the somatostatin receptor expressed by activated macrophages implicated in the first phase of aortic valve pathogenesis. It may therefore provide a better understanding of the role of inflammation due to its more favorable noise-to-signal profile, which is a drawback of 18F-FDG (lack of specificity) [(275)].

^{68}Ga-NOTA-anti-MMR-Nb: This radiotracer is linked to a nano-antibody targeting the macrophage mannose receptor (MMR or CD206) to assess macrophage polarization. The extent of infiltration by M2 macrophages, which are apparently involved in tissue remodeling, could also serve as another strategy to evaluate inflammation in aortic valves, as an alternative to 18F-FDG.

Similar to how 18F-FDG is used in oncology to assess metabolic remission, metabolic imaging in cardiology, particularly in aortic stenosis, holds considerable promise (provided that effective therapies are developed). Molecular imaging could ultimately change the way we manage valve disease. However, several significant challenges still hinder its widespread clinical adoption. These include radiation exposure, high imaging costs, and limited availability of PET scanners. In addition, cardiac PET imaging faces technical hurdles such as motion artifacts — arising from cardiac, respiratory, and patient movement — as well as long acquisition times, which collectively impair quantitative accuracy.

Part 8. REFERENCES

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Part 9. PUBLICATIONS

Boute M, **De Azevedo D**, de Terwangne C et al. Surgical and transcatheter aortic valve replacement align survival with general population expectations: insights from standardized mortality ratios. Frontiers in Cardiovascular Medicine 2025; Volume 12 - 2025.

De Azevedo D., Boute M., Tribouilloy C., Maréchaux S., Pouleur AC., Bohbot Y., Rusinaru D., Altes A., Thellier N., Beauloye C., Pasquet A., Gerber B., de Kerchove L., Vanoverschelde JL, Vancraeynest D. Quantifying the survival loss linked to late therapeutic indication in high-gradient severe aortic stenosis. JACC: Advances, 2024

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